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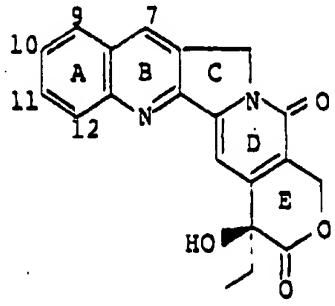
Description

The present invention relates to new camptothecin derivatives useful as medicaments or intermediates therefor and a process for preparing the new camptothecin derivatives. More particularly, the present invention relates to new camptothecin derivatives carrying, in addition to a $C_1 - C_8$ alkyl group in 7-position thereof, one or more substituents in 9-, 10-, 11- and/or 12-position thereof which are useful as anti-tumor drugs or intermediates therefor as well as a process for preparing the new camptothecin derivatives wherein 1,5-dioxo(5'-ethyl-2'H,5'H,6'H-6-oxopyrano)[3',4'-f]-Δ6(8)-tetrahydroindolidine is condensed with an o-acyl-aniline compound (or more specifically, a $C_1 - C_8$ alkanophenone carrying an amino group in 2-position of its phenyl group and one or more substituents in 3-, 4-, 5- and/or 6-position thereof) and the resultant corresponding 20-deoxy-camptothecin derivative is oxidized.

Camptothecin represented by the following structural formula:



is an alkaloid extracted and isolated from Camptotheca accuminata (Nyssaceae), which has a pentacyclic structure consisting of a characteristic fused 5-ring system consisting of quinoline (rings A and B), pyrroline (ring C), α-pyridone (ring D) and a six-membered lactone (ring E) and is distinguished by displaying a strong inhibitory activity toward biosynthesis of nucleic acid. In addition, camptothecin is a unique anti-tumor substance characterized by its rapid and reversible action, its lack of any cross-tolerance with the existing anti-tumor agents and by exhibiting a strong anti-tumor activity against experimentally transplanted carcinoma such as leukemia L-1210 in mice or Walker 256 tumor in rats. Although camptothecin is still regarded as one of the most potent substances possessing anti-tumor activity, the use of this compound itself for clinical treatments is significantly limited because of high toxicity. Moreover, camptothecin and the majority of derivatives thereof involve a problem of poor solubility in case of administration as medicaments.

For these reasons, a number of studies have been made heretofore not only to reduce toxicity of camptothecin while maintaining its anti-tumor activity by converting camptothecin chemically into its derivatives but also to make improvement in solubility of camptothecin and derivatives thereof by chemical modifications of the camptothecin molecule or substituents therein. However, any chemical modification of the ring D and/or E of camptothecin, including ring-opening reactions of the ring D and/or E, revealed only failure in maintaining anti-tumor activity and very poor improvement in toxicity [J. Med. Chem., 19 (1976), 675]. From the chemotherapeutic point of view, therefore, it is of importance that the chemical modifications of camptothecin should be restricted in the rings A, B and C without effecting any change in the rings D and E Which are believed to be the essential structural elements for the expression of the above mentioned characteristic biological activities.

EP-A 074 256 discloses 7- and/or 10-substituted camptothecin derivatives with antitumor activity and low toxicity.

JP-A-6185389 describes the preparation of a 7- and/or 12-substituted camptothecin derivative which can be used as antitumor agent.

EP-A 220 601 discloses pyranoindolizine derivatives which are useful as intermediates for the synthesis of camptothecin derivatives.

The present inventors made extensive researches for d veloping a new class of camptothecin derivatives with co-work rs on the basis of the above mentioned knowledge and found a process for preparing 5- and 7-substitut d camptothecin derivatives (U.S. Patent 4,399,282), a process for pr paring various derivatives from thes 5- and 7-substituted camptothecin derivativ s (U.S. Patents 4,399,276 and 4,399,282), a process for pr paring 10-substituted camptothecin derivatives (U.S. Patents 4,473,692 and

4,545,880), a process for preparing camptothecin derivatives disubstituted in 7-position end 9-, 10- or 11-position (U.S. Patent 4,604,463) and a process for preparing 5- and/or 7-substitut d camptothecin N-oxide derivatives (U.S. Patent 4,513,138).

It was made clear from the studies on the various camptothecin derivatives prepared heretofore that introduction of an alkyl group into the 7-position of camptothecin tends to enhance anti-tumor activity. It is also noted that all of the camptothecin derivatives disclosed in these prior art references are derived from camptothecin or its derivatives but are not synthesized from other compounds which are not in possession of the fundamental structure or camptothecin.

For further extensive research based on these facts for sounding possibility of developing other new camptothecin derivatives also useful as anti-tumor agents or intermediates therefor and finding a new route for synthesizing camptothecin derivatives, there is still a great demand in the art for developing a further new class of camptothecin derivatives carrying an alkyl group in 7-position thereof and various substituents in the ring A thereof according to a process quite different from the processes disclosed in the prior art references above mentioned.

Accordingly, it is an object of the present invention to provide new camptothecin derivatives carrying, in addition to an alkyl group in 7-position thereof, one or more substituents in 9-, 10-, 11- and/or 12-position on the ring A thereof.

It is another object of the present invention to provide new camptothecin derivatives possessing strong anti-tumor activity with extremely weak toxicity.

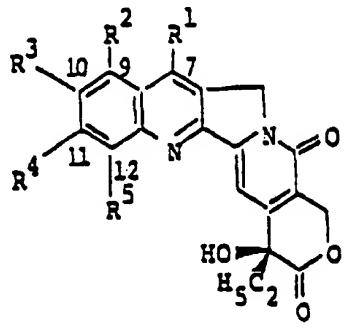
It is still another object of the present invention to provide a process for the preparation of new camptothecin derivatives carrying, an alkyl group in 7-position thereof, one or more substituents in 9-, 10-, 11- and/or 12-position on the ring A thereof according to a simple and economical procedure.

It is further object of the present invention to provide a new means for synthesizing compounds having the fundamental structure of camptothecin from a starting material different from camptothecin.

Other objects, features and advantages of the present invention will become apparent more fully from the following description.

As a result of extensive researches made by the present inventors, it has now been found that new camptothecin derivatives carrying, in addition to an alkyl group in 7-position thereof, one or more substituents in 9- , 10-, 11- and/or 12-position on the ring A thereof are also strong in anti-tumor activity and can be synthesized totally from 1,5-dioxo-(5'-ethyl-2'H,5'H,6'H-6-oxopyrano)[3',4'-f]-Δ6(8)-tetrahydroindolidine and an o-acyl-aniline compound. The present invention has been accomplished on the basis of the above finding.

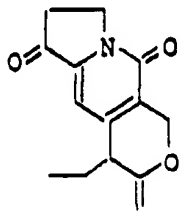
In accordance with the present invention, there are provided new camptothecin derivatives represented by the general formula:



(I)

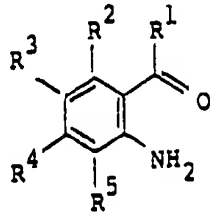
wherein R^1 represents a C_1-C_8 alkyl group, R^2 represents a hydrogen atom or an amino, hydroxyl, C_1-C_8 acylamino or C_1-C_8 alkoxy group, R^3 represents a hydrogen or halogen atom or a C_1-C_8 alkyl, hydroxyl, C_1-C_8 alkoxy, nitro, amino, cyano or di(C_1-C_8 alkyl)amino group, R^4 represents a hydrogen or halogen atom or a C_1-C_8 alkyl, hydroxyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, amino, cyano, C_1-C_8 alkylamino or di-(C_1-C_8 alkyl)amino group, and R^5 represents a hydrogen or halogen atom or a hydroxyl or C_1-C_8 alkoxy group, with th proviso that not all of the R^2, R^3, R^4 and R^5 substituents ar simultaneously a hydrogen atom and also than if any one of th R^2, R^3, R^4 and R^5 is a hydroxyl or C_1-C_8 alkoxy group, not all of the other three substituents are simultaneously a hydrogen atom.

In accordance with the present invention, there is also provided a process for the preparation of new camptothecin derivatives of th general formula (I) which comprises condensing 1,5-dioxo(5'-ethyl-2'H,5'H,6'H-6-oxopyrano)[3',4'-f]-Δ6(8)-tetrahydroindolidine of th formula:



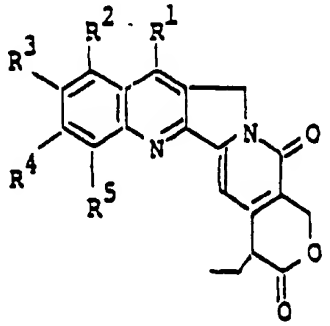
(II)

with an o-acyl-aniline compound of the general formula:



(III)

wherein R^1, R^2, R^3, R^4 and R^5 have the same meanings as given above,
and oxidizing the resultant 20-deoxy-camptothecin derivative of the general formula:



(IV)

wherein R^1, R^2, R^3, R^4 and R^5 have the same meanings as given above,
with oxygen in the presence of cupric ions, and if desired, converting in the resultant camptothecin derivative of the general formula (I) any alkoxy group into the free hydroxyl group and any free amino group into a C_1-C_8 acylamino group.

The present invention is featured by providing new camptothecin derivatives carrying a lower alkyl group in 7-position thereof and at least one substituent in 9-, 10-, 11- and/or 12-position on the fused benzene ring A with the proviso that if any one of the substituents is a hydroxyl or C_1-C_8 alkoxy group, at least one of the other substituents should be one other than hydrogen atom. The present invention is also featured by preparing the camptothecin derivatives without chemical modifications of the starting compound having the skeleton of camptothecin.

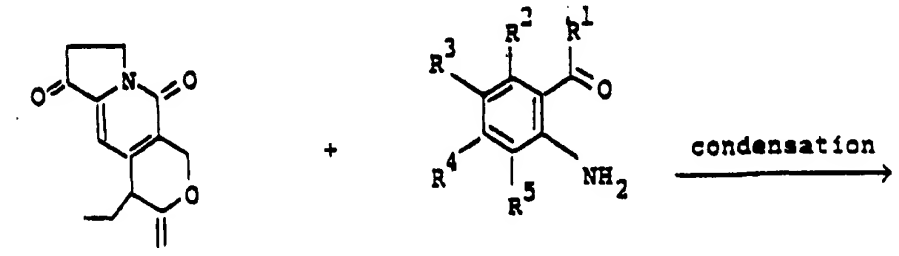
In the new camptoth cin derivatives of the general formula (I), th starting o-acyl-aniline compounds of the g neral formula (III) and th 20-deoxy intermediat of th gen ral formula (IV), the C_1-C_8 alkyl group preferably contains 1-4 carbon atoms. The alkyl group has generally a straight chain but may b branched at any position if the alkyl group has at least 3 carbon atoms. Illustrative of the C_1-C_8 alkyl group are, for example, methyl, ethyl, propyl, isopropyl, tert- butyl, pentyl, hexyl, heptyl and octyl. Preferable ar

methyl, ethyl, propyl, isopropyl and butyl. This definition also applies to a C_1-C_8 alkyl moiety in the C_1-C_8 alkoxy, alkylthio and di(C_1-C_8 alkyl)amino groups. Accordingly, the C_1-C_8 alkoxy group, for exampl , has preferably 1-4 carbon atoms in its alkyl moiety which may have a straight or branched chain. Likewis , the C_1-C_8 acyl group had preferably 1-4 carbon atoms in its molecule, typical examples of which include acetyl, propionyl, butyryl, pentanoyl, hexanoyl and octanoyl. The halogen atom is an important substituent and is selected normally from fluorine, chlorine and bromine atoms.

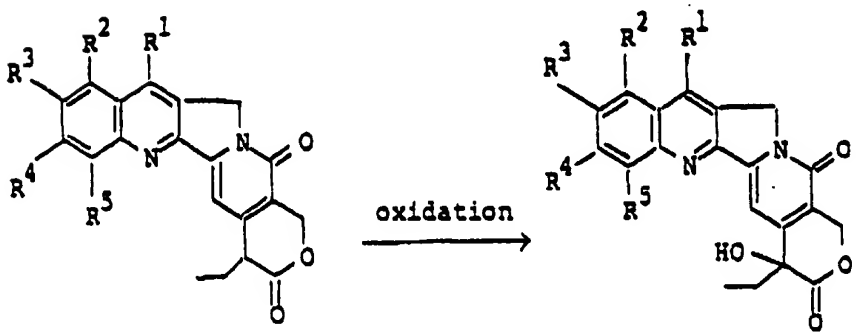
In case at least one substituent on the benzene ring A of the camptothecin derivatives is a C_1-C_8 alkyl group, this group may be same as or different from the C_1-C_8 alkyl group R^1 located in 7-position of the camptothecin derivatives. In case plural substituents of the same kind exist, they may be same or different. For example, when R^2 and R^3 are halogen atoms, they may be the same or different.

Among the new camptothecin derivatives of this invention represented by the general formula (I), some are extremely strong in anti-tumor activity and so can be used as anti-tumor drugs while some are not so strong in anti-tumor activity but can be used as intermediates for preparing anti-tumor drugs. Illustrative of the new camptothecin derivatives of this invention are, for example, 7-methyl-10-fluoro-camptothecin (for brevity, the term "camptothecin" will be referred to in this sentence simply as CPT), 7-methyl-10-chloro-CPT, 7-methyl-10-bromo-CPT, 7-methyl-11-fluoro-CPT, 7-methyl-11-chloro-CPT, 7-methyl-11-bromo-CPT, 7-methyl-12-fluoro-CPT, 7-methyl-12-chloro-CPT, 7-methyl-12-bromo-CPT, 7-methyl-9,10-dimethoxy (or -dihydroxy)-CPT, 7-methyl-9,12-dimethoxy (or -dihydroxy)-CPT, 7-methyl-10,11-dimethoxy (or -dihydroxy)-CPT, 7-methyl-9-hydroxy-12-methoxy-CPT, 7-methyl-9,10,11-trimethoxy-CPT, 7-methoxy-9-amino-CPT, 7-methoxy-9-acetoamino-CPT, 7-methyl-10-amino-CPT, 7-methyl-10-dimethylamino-CPT, 7-methyl-11-amino-CPT, 7,10-dimethyl-CPT, 7-methyl-11-ethyl-CPT, 7-methyl-10-cyano-CPT, 7-methyl-10-nitro-CPT, 7-methyl-11-methylthio-CPT, and the corresponding 7-ethyl-, 7-propyl-, 7-isopropyl- and 7-butyl-analogues.

According to the process of this invention, the new camptothecin derivative of the general formula (I) can be prepared according to the following reaction scheme:



(II) (III)



(IV) (I)

The reactions themselves (Friedländer's condensation followed by oxidation) adopt d in the process of this invention are known in this art. The compound of the formula (II), i.e. 1,5-dioxo(5'-ethyl-2'H,5'H,6'H-6-oxopyrano) [3',4-f-]-Δ6(8)-tetrahydroindolidine, is known and can b prepared according to the method disclosed in M.C. Wani et al., J. Med. Chem., 23, 554 (1980). The majority of the o-acyl-aniline compounds (or more specifically, a lower alkano phenone carrying an amino group in 2-position of its benzene ring and one or more substituents in 3-, 4-, 5- and/or 6-position thereof) is known and commercially available. However, the compounds of the general formula (II) can be prepared at need according to the methods known per se.

The condensation reaction of the compound of the formula (II) with the compound of the general formula (III) is carried out under the conditions customarily used in Friedländer's reaction. Thus, the reactants are dissolved in a solvent inert to the reaction and heated under reflux in the presence of a dehydration catalyst. As the reaction itself is a dehydro-condensation reaction, the solvent utilizable therefor is preferably an aromatic hydrocarbon which forms a heterogenous phase to water and can be distilled with water, forming an azeotrope. Preferable examples of the aromatic hydrocarbon include benzene, toluene and xylene which are used singly or as a mixture, considering the relation between the reaction temperature and their boiling points. It is preferable to use a Dean-Stark apparatus to facilitate separation of water formed during the condensation reaction. The time required for the reaction varies according to the reactants but is usually from 8 hours to 2 days. After completion of the reaction, the solvent is removed from the reaction mixture preferably under reduced pressure and the residue is washed with a solvent such as chloroform-ether. The condensation product thus obtained, i.e. the corresponding 20-deoxy camptothecin derivative of the general formula (IV) is usually used as such for the subsequent step without necessity of purification.

A preferable example of the dehydration catalyst used in this case is p-toluenesulfonic acid. The reaction temperature is generally maintained above the boiling point of water or its azeotrope with the inert solvent.

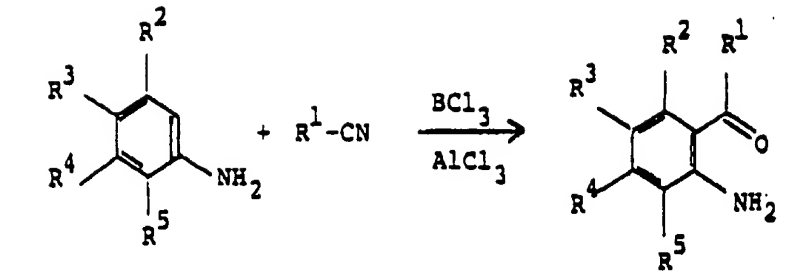
The 20-deoxy camptothecin derivative of the general formula (IV) is then oxidized to the derivative of the general formula (I). For this, the 20-deoxy derivative is dissolved in a solvent inert to the reaction. A preferable solvent for this purpose is dimethylformamide, diethylformamide or dimethylsulfoxide. A cupric salt such as cupric chloride, cupric acetate or cupric nitrate in a proper amount is then dissolved in the solution and gaseous oxygen is blown into the mixture until the starting 20-deoxy derivative is completely oxidized. After completion of the reaction, the solvent used is removed by distillation and the residual product is subjected to purification by way of thin layer or column chromatography using chloroform-methanol as eluent.

The substituents in the camptothecin derivatives of the general formula (I) thus obtained may be converted, if desired, into other substituents. For example, the C_1-C_8 alkoxy group or groups can be converted completely or partially into the free hydroxyl group by heating the C_1-C_8 alkoxy derivative under reflux in a solvent inert to the reaction, such as 1,1,2,2-tetrachloroethane, toluene or benzene in the presence of aluminum salt such as aluminum chloride or aluminum bromide. Alternatively, the C_1-C_8 alkoxy derivative may be boiled with a concentrated hydrohalic acid such as 48% hydrobromic acid for several hours to effect solvolysis.

The camptothecin derivatives carrying a free amino group as substituent can be treated with an acylating agent to convert their free amino group into the corresponding acylamino group.

For this, the camptothecin derivative carrying the free amino group is dissolved in a solvent inert to the reaction and is reacted with 3-5 equivalents of an acylating agent in the presence of a tertiary amine as a base at a temperature ranging from ice-cooling temperature to room temperature. Illustrative of the solvent utilizable for this acylation are, for example, methylene chloride, chloroform, dioxane, tetrahydrofuran, acetonitrile and dimethylsulfoxide. Utilizable as the tertiary amine are, for example, triethylamine, pyridine, picoline and pyrrolidine. A lower alkanoic halide such as acetyl chloride or a lower alkanoic anhydride such as acetic anhydride can be used as the acylating agent.

The o-acyl-aniline compound of the general formula (III) as one of the reactants for the condensation reaction may be prepared, for example, according to a process as disclosed in T. Sugasawa, T. Toyoda, M. Adachi and K. Sasakura, J. Am. Chem. Soc., 100, 4842 (1978) and as shown in the following reaction scheme:



(V) (III)

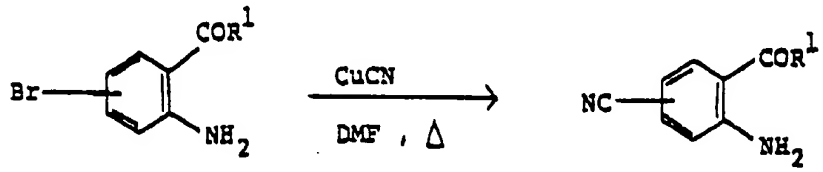
Thus, 1.1 equivalent of boron trichloride is dissolved in an inert solvent such as benzene, toluene, dichloroethane or tetrachloroethane, preferably benzene, and 1 equivalent of an aniline derivative (V) is added with ice-cooling. To the resultant aniline-boron trichloride adduct is added 1 to 2 equivalents of a nitrile (R-CN: lower alkyl- or branched lower alkylnitrile), and 1.1 equivalent of aluminum chloride is then added. The mixture is heated under reflux for 8 to 20 hours and then ice-cooled. After addition of 2N-hydrochloric acid, the mixture is stirred at 80°C for one hour. After cooling, water is added to the reaction mixture.

In case the end product exists in the organic phase, the organic phase is separated and the aqueous phase is further extracted with an organic solvent such as benzene or ethyl acetate. The extract and the organic phase are combined and washed with water.

Where the product is in the aqueous phase, the organic phase is discarded, and the aqueous phase is further washed with an organic solvent such as benzene or ethyl acetate. The aqueous phase is made alkaline with an aqueous solution of a caustic alkali, extracted several times with an organic solvent as mentioned above, and washed with water.

The organic phase obtained in either case is then dried with a drying agent such as anhydrous sodium sulfate or anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue is recrystallized from an appropriate solvent such as n-hexane, chloroform-n-hexane or ether, or is first separated and purified by column chromatography on silica gel (eluent : toluene-ethyl acetate system, chloroform-n-hexane system, benzene-n-hexane system) and then recrystallized from an appropriate solvent.

Cyano-substituted derivatives can be prepared by reacting a corresponding bromo-substituted derivative dissolved in a solvent inert to the reaction such as dimethyl-formamide with cuprous cyanide under heat in nitrogen atmosphere, according to the following reaction scheme:



Accordingly, selection of the substituents R^1 - R^5 in the camptothecin derivatives can advantageously be made at the stage of preparing the compound of the general formula (III) although some substituents (e.g. alkoxy or amino group) may optionally be converted into other substituents even after the main condensation reaction.

The anti-tumor activity of the camptothecin derivatives of the present invention can be demonstrated by the following Experiments wherein the camptothecin derivatives of this invention were subjected together with similar comparativ compounds to screening with KB and L1210 cells. The results are shown below.

[METHODS]

The cells used for the experiments were KB cells, i.e. cultured cell strain derived from human nasopharyngeal cancer, and mouse leukemia-derived L1210 cells (Dainippon Pharmaceutical, Japan) both being kept freezed. KB cells were cultured in Eagle's minimal essential medium (Nissui Pharmaceutical, Japan) with 10% calf serum (GIBCO Laboratories) and L1210 cells were cultured in RPMI 1640 medium (Nissui Pharmaceutical) with 10% fetal bovine serum (GIBCO Laboratories). Both cells were cultured at 37°C in carbon dioxide gas incubator (5% CO_2).

The cell growth-inhibition test with the drugs was carried out in the following manner based on the random screening method by Cancer Chemotherapy Center, Japanese Foundation for Cancer Research [Report of Special Committee on anticancer agents screening, Special Cancer Research Administration Group (Gan-Tokubetsu-Kenkyu Sokatsu-Han), Ministry of Education, Jpn. J. Cancer Chemother., 11-(9), Part II : p1905, 1984]. In the case of KB cells, the cells were diluted to give a 2 x 10^4/ml culture on day 1. 3 ml of the culture was placed in a 60 mm plastic Petri dish. On day 0, the medium was replaced with culture medium containing each camptothecin derivative in an appropriate concentration and the cells were incubated for additional 3 days. On day 3, the cells were detached from the Petri dish with 0.25% trypsin (GIBCO Laboratories) and the cells were counted with a Coulter Counter (Type ZM, Coulter Electronics). In the cage of L1210 cells, the cells were diluted to give a 4 x 10^4/ml culture on day 0. 0.5 ml portion of the culture was placed in each well of a 24-well plate, and pre-cultured for 3 hours. 0.5 Ml of culture medium containing each camptothecin derivative in an appropriate concentration was added thereto and incubated for 3 days, and the cells were counted on day 3 with the Coulter counter.

The growth-inhibition rate was calculated by subtracting the number of treated cells from the number of untreated control cells to give the genuine growth-inhibition rate. The 50% effective dose (ED_{50}) was calculated from the obtained growth-inhibition curve by interpolation. The camptothecin derivatives were respectively dissolved in dimethylsulfoxide (DMSO) at a concentration of 1 mg/ml and kept at -20°C. Under this condition, the effect of DMSO on ED_{50} was not observed.

[RESULTS]

Camptothecin derivatives tested (with R^1-R^4 in the formula indicated)	KB cells ED_{50} (ng/ml)	L1210 cells ED_{50} (ng/ml)
Experiment 1		
R^1 = Me R^4 = Br	0.44	1.2
R^1 = Et R^3 = Me	0.46	1.4
Camptothecin	1.6	5.0
7-ethyl-10-hydroxy-camptothecin	0.52	3.9
Experiment 2		
R^1 = Et R^3 = Br	0.42	1.0
R^1 = Et R^3 = Cl	0.35	1.1
R^1 = Et R^3 = F	1.0	2.2
R^1 = Et R^4 = Br	1.1	1.8
R^1 = Et R^4 = Cl	0.48	1.1
R^1 = Et R^4 = F	0.17	0.43
Camptothecin	1.3	1.6
7-ethyl-10-hydroxy-camptothecin	0.47	3.2
Experiment 3		
R^1 = Pr R^3 = Me	1.2	1.9
R^1 = Pr R^4 = Cl	0.62	1.5
R^1 = Bu R^3 = Br	1.1	1.5
Camptothecin	1.5	4.7
7-ethyl-10-hydroxy-camptothecin	0.48	3.4

Experiment 4		
R^1 = Et R^3 = R^4 = Cl	0.54	0.61
Camptothecin	1.5	4.1
7-ethyl-10-hydroxy-camptothecin	0.51	2.4
Experiment 5		
R^1 = Et R^3 = NH_2	0.26	1.1
Camptothecin	1.5	4.8
7-ethyl-10-hydroxy-camptothecin	0.47	3.6
Experiment 6		
R^1 = Et R^3 = OCH_3 R^4 = F	0.14	0.40
R^1 = Et R^3 = OH R^4 = F	0.31	2.2
R^1 = Et R^4 = CH_3NH_2.HCl	0.42	2.3
Camptothecin	1.4	4.3
7-ethyl-10-hydroxy-camptothecin	0.45	3.7
Experiment 7		
R^1 = Et R^3 = CH_3 R^4 = F	0.17	0.37
R^1 = Et R^3 = R^4 = F	0.31	0.55
Camptothecin	1.2	4.1
7-ethyl-10-hydroxy-camptothecin	0.44	3.1

Examples of the preparation of novel camptothecin derivatives are given below together with data from analytical instruments.

Example 1

7 - Methyl - 11 - bromocamptothecin

1,5 - Dioxo(5' - ethyl - 2'H,5'H,6'H - 6 - oxopyrano) [3',4' - f] - Δ6(8) tetrahydroindolidine (1.00 g, 4.06 mmol), 2 - amino - 4 - bromoacetophenone (957 mg, 4.47 mmol) and p - toluene - sulfonic acid (320 mg) are dissolved in 200 ml of toluene and boiled under reflux for 24 hours using a Dean - Stark apparatus. The solvent is distilled off under reduced pressur and the residue is washed with chloroform - ether, and then

dissolved in 240 ml of dimethylformamide. 2.37 g of cupric chloride and 0.71 ml of 40% aqueous solution of dimethylamin are added to the solution, and oxygen gas is then blown into the mixture until the starting materials are no longer observed on the thin layer chromatogram. After completion of the reaction, the solvents are distilled off under reduced pressure, and the residue is subjected to isolation and purification by column chromatography on silica gel (chloroform - methanol system) whereby 1.02 g (55.4%) of the title compound is obtained.

M.P 264 - 265 °C (with decomposition: referred to hereinafter as "d")

IR (KBr) : 3397, 2965, 2925, 2865, 1750, 1656, 1596, 1156.

NMR (DMSO - d_6) δppm:

0.89 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.82 - 1.93 (2H, m, 20 - CH_2CH_3)
2.75 (3H, s, 7 - CH_3)
5.21 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.52 (1H, br.s, 20 - OH)
7.30 (1H, s, 14 - H)
7.80 (1H, dd, 10 - H)
8.15 (1H, d, $J_{9,10}$ = 9.2Hz, 9 - H)
8.31 (1H, d, $J_{10,12}$ = 1.8Hz, 12 - H)

Example 2

7 - Methyl - 12 - fluorocamptothecin

Using 2 - amino - 3 - fluoroacetophenone (see Preparative Example 21 : 682 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.65 g (42.2%) of the title compound is obtained.

MP 256 - 258.5 °C (d)

IR (KBr): 3379, 1757, 1657, 1621, 1150.

NMR (DMSO - d_6), δppm:

0.90 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.83 - 1.94 (2H, m, 20 - CH_2CH_3)
2.77 (3H, s, 7 - CH_3)
5.24 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.54 (1H, br.s, 20 - OH)
7.31 (1H, s, 14 - H)
7.64 - 7.68 (2H, m, 10 and 11 - H)
8.00 - 8.03 (1H, m, 9 - H)

Example 3

7 - Ethyl - 9 - aminocamptothecin

Using 2,6 - diaminopropiophenone (see Preparative Example 20: 733 mg, 4.47 mmol) and p - toluenesulfonic acid (1.2 g), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.32 g (20.5%) of the title compound is obtained.

MP 229 - 231 °C (d)

IR (KBr): 3360, 2958, 1744, 1650, 1592, 1160.

NMR (DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.36 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.81 - 1.91 (2H, m, 20 - CH_2CH_3)
3.31 (2H, q, 7 - CH_2CH_3)
5.29 (2H, s, 5 - CH_2)
5.42 (2H, s, 17 - CH_2 -)
6.48 (1H, s, 20 - OH)
6.97 (1H, d, $J_{10,11}$ = 7.7Hz, 10 - H)

7.26 (1H, s, 14-H)
7.43 (1H, d, $J_{11,12}$ = 7.7Hz, 12-H)
7.50 (1H, dd, 11-H)

Example 4

7-Ethyl-9-acetaminocamptothecin

100 mg (0.26 mmol) of 7-ethyl-9-aminocamptothecin is suspended in 30 ml of methylene chloride. To the suspension are added 1 ml of triethylamine and 60 mg (0.76 mmol) of acetyl chloride in that order, and the mixture is stirred at room temperature for one day. The mixture is evaporated under reduced pressure to dryness and the residue is isolated and purified by column chromatography on silica gel (eluent: chloroform-methanol 50:1) and washed with ethanol whereby 10 mg (9.0%) of the title compound is obtained as pale yellow crystals.

MP 205-210°C (d)
IR (KBr): 3340, 2960, 2920, 1740, 1656, 1598, 1159.
NMR (DMSO-d_6) δppm:
0.89 (3H, t, J = 7.3Hz, 20-CH_2CH_3)
1.22 (3H, t, J = 7.7Hz, 7-CH_2CH_3)
1.83-1.93 (2H, m, 20-CH_2CH_3)
2.14 (3H, s, $COCH_3$)
3.28 (2H, q, 7-CH_2CH_3)
5.32 (2H, s, 5-CH_2-)
5.43 (2H, s, 17-CH_2-)
6.52 (1H, s, 20-OH)
7.32 (1H, s, 14-H)
7.49 (1H, d, $J_{10,11}$ = 7.7Hz, 10-H)
7.81 (1H, dd, 11-H)
8.11 (1H, d, $J_{11,12}$ = 8.1Hz, 12-H)
10.11 (1H, s, -$NHCOCH_3$)

Example 5

7-Ethyl-10-fluorocamptothecin

Using 2-amino-5-fluoropropiophenone (see Preparative Example 8;, 747 mg, 4.47 mmol), the reaction followed by the after-treatment is carried out in the same manner as in Example 1 whereby 0.92 g (57.3%) of the title compound is obtained.

MP 240-242°C (d)
IR (KBr): 3363, 2966, 1751, 1655, 1605, 1510, 1233, 1155.
NMR (DMSO-d_6) δppm:
0.89 (3H, t, J = 7.3Hz, 20-CH_2CH_3)
1.29 (3H, t, J = 7.7Hz, 7-CH_2CH_3)
1.79-1.95 (2H, m, 20-CH_2CH_3)
3.18 (2H, q, 7-CH_2CH_3)
5.29 (2H, s, 5-CH_2-)
5.43 (2H, s, 17-CH_2-)
6.51 (1H, s, 20-OH)
7.31 (1H, s, 14-H)
7.75 (1H, ddd, $J_{9,11}$ = 2.9Hz, $J_{11,12}$ = 9.2Hz, $J_{11,F}$ = 11.0Hz, 11-H)
8.02 (1H, dd, $J_{9,F}$ = 10.6Hz, 9-H)
8.21 (1H, dd, $J_{12,F}$ = 5.5Hz, 12-H)

Example 6

7 - Ethyl - 10 - chlorocamptothecin

Using 2 - amino - 5 - chloropropiophenone (see Preparative Example 9: 821 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.70 g (42.1%) of the title compound is obtained.

MP 238 - 239 °C (d)

IR (KBr): 3314, 2968, 1753, 1653, 1593.

NMR (DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.30 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.78 - 1.97 (2H, m, 20 - CH_2CH_3)
3.21 (2H, q, 7 - CH_2CH_3)
5.30 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.52 (1H, s, 20 - OH)
7.32 (1H, s, 14 - H)
7.85 (1H, dd, $J_{9,11}$ = 2.2Hz, $J_{11,12}$ = 9,2Hz, 11 - H)
8.16 (1H, d, 12 - H)
8.31 (1H, d, 9 - H)

Example 7

7 - Ethyl - 10 - bromocamptothecin

Using 2 - amino - 5 - bromopropiophenone (see Preparative Example 10: 1.02 g, 4,47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 1.02 g (55.4%) of the title compound is obtained.

MP 241 - 243 °C (d)

IR (KBr): 3500, 3340, 2967, 1736, 1654, 1608, 1451, 1149.

NMR (DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.30 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.78 - 1.97 (2H, m, 20 - CH_2CH_3)
3.21 (2H, q, 7 - CH_2CH_3)
5.32 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.52 (1H, s, 20 - OH)
7.33 (1H, s, 14 - H)
7.96 (1H, dd, $J_{9,11}$ = 2.2Hz, $J_{11,12}$ = 9.2Hz, 11 - H)
8.09 (1H, d, 12 - H)
8.46 (1H, d, 9 - H)

Example 8

7 - Ethyl - 10 - methylcamptothecin

Using 2 - amino - 5 - methylpropiophenone (see Preparative Example 11: 728 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.96 g (60.9%) of the title compound is obtained.

MP 245 - 247 °C (d)

IR (KBr): 3400, 2965, 1751, 1651, 1590, 1157.

NMR (DMSO - d_6) δppm:

0.89 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.31 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.81 - 1.93 (2H, m, 20 - CH_2CH_3)
2.58 (3H, s, 10 - CH_3)

3.19 (2H, q, 7 - CH_2CH_3)
5.28 (2H, s, 5 - $\overline{CH_2}$ -)
5.43 (2H, s, 17 - CH_2 -)
6.50 (1H, s, 20 - OH)
7.30 (1H, s, 14 - H)
7.68 (1H, dd $J_{9,11}$ = 1.8Hz, $J_{11,12}$ = 8.5Hz, 11 - H)
8.03 (1H, d, 9 - H)
8.05 (1H, d, 12 - H)

Example 9

7 - Ethyl - 10 - cyanocamptothecin

Using 2 - amino - 5 - cyanopropiophenone (see Preparative Example 31: 779 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.51 g (31.1%) of the title compound is obtained.

MP 234 - 237 °C (d)
IR (KBr): 3410, 2220, 1744, 1657, 1601, 1154.
NMR (DMSO - d_6) δppm:
0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.31 (3H, t, J = 7.7Hz, 7 - $CH_2\overline{CH_3}$)
1.79 - 1.96 (2H, m, 20 - $CH_2\overline{CH_3}$)
3.25 (2H, q, 7 - CH_2CH_3)
5.36 (2H, s, 5 - $\overline{CH_2}$ -)
5.44 (2H, s, 17 - CH_2 -)
6.55 (1H, s, 20 - OH)
7.35 (1H, s, 14 - H)
8.00 (1H, dd, $J_{9,11}$ = 1.8Hz, $J_{11,12}$ = 8.8Hz, 11 - H)
8.45 (1H, d, 12 - H)
8.70 (1H, d, 9 - H)

Example 10

7 - Ethyl - 10 - nitrocamptothecin

Using 2 - amino - 5 - nitropropiophenone (see Preparative Example 29: 894 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.18 g (10.4%) of the title compound is obtained.

MP > 360 °C
IR (KBr): 3415, 1750, 1652, 1598, 1340.
NMR (DMSO - d_6) δppm:
0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.35 (3H, t, J = 8.1Hz, 7 - $CH_2\overline{CH_3}$)
1.82 - 1.94 (2H, m, 20 - $CH_2\overline{CH_3}$)
3.33 (2H, q, 7 - CH_2CH_3)
5.38 (2H, s, 5 - $\overline{CH_2}$ -)
5.45 (2H, s, 17 - CH_2 -)
6.55 (1H, s, 20 - OH)
7.39 (1H, s, 14 - H)
8.35 (1H, d, $J_{11,12}$ = 9.5Hz, 12 - H)
8.53 (1H, dd, 11 - H)
9.08 (1H, d, $J_{9,11}$ = 2.9Hz, 9 - H)

Example 11

7 - Ethyl - 10 - aminocamptothecin

Using 2,5 - diaminopropiophenone (734 mg, 4.47 mmol) and p - toluenesulfonic acid (1.2 g), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.22 g (14.1%) of the title compound is obtained.

MP 215 - 217° C (d)

IR (KBr): 3410, 3330, 2960, 1740, 1646, 1632, 1580, 1570, 1512, 1164.

NMR (DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.29 (3H, t, J = 8.1Hz, 7 - CH_2CH_3)
1.79 - 1.91 (2H, m, 20 - CH_2CH_3)
3.01 (2H, q, 7 - CH_2CH_3)
5.22 (2H, s, 5 - CH_2 -)
5.40 (2H, d, J_{gem} = 2.9Hz, 17 - CH_2 -)
5.93 (2H, s, 10 - NH_2)
6.44 (1H, s, 20 - OH)
7.07 (1H, d, $J_{9,11}$ = 2.9Hz, 9 - H)
7.18 (1H, s, 14 - H)
7.24 (1H, dd, 11 - H)
7.84 (1H, d, $J_{11,12}$ = 8.8Hz, 12 - H)

Example 12

7 - Ethyl - 10 - dimethylaminocamptothecin

Using 2 - amino - 5 - dimethylaminopropiophenone (see Preparative Example 19: 858 mg, 4.47 mmol) and p - toluenesulfonic acid (1.2 g), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.59 (34.9%) of the title compound is obtained.

MP 270 - 271.5° C (d)

IR (KBr): 3390, 2960, 1740, 1646, 1618, 1586, 1551, 1162.

NMR (DMSO - d_6) δppm:

0.88 (3H, t, J = 7.0Hz, 20 - CH_2CH_3)
1.31 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.81 - 1.92 (2H, m, 20 - CH_2CH_3)
3.11 (8H, m, 10 - $N(CH_3)_2$ and 7 - CH_2CH_3)
5.22 (2H, s, 5 - CH_2 -)
5.41 (2H, d, J_{gem} = 1.8Hz, 17 - CH_2 -)
6.45 (1H, s, 20 - OH)
6.96 (1H, d, $J_{9,11}$ = 2.6Hz, 9 - H)
7.20 (1H, s, 14 - H)
7.53 (1H, dd, 11 - H)
7.92 (1H, d, $J_{11,12}$ = 9.2Hz, 12 - H)

Example 13

7 - Ethyl - 11 - fluorocamptothecin

Using 2 - amino - 4 - fluoropropiophenone (see Preparative Example 1: 747 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.65 g (40.9%) of the title compound is obtained.

MP 196 - 198° C (d)

IR (KBr): 3335, 3080, 2960, 2920, 1746, 1652, 1597, 1509, 1214, 1154.

NMR (DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.32 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.78 - 1.95 (2H, m, 20 - CH_2CH_3)

3.23 (2H, q, 7 - CH_2CH_3)
5.31 (2H, s, 5 - CH_2 -)
5.44 (2H, s, 17 - CH_2 -)
6.52 (1H, br.s, 20 - OH)
7.33 (1H, s, 14 - H)
7.65 (1H, ddd, $J_{9,10}$ = 9.2Hz, $J_{10,12}$ = 2.9Hz, $J_{10,F}$ = 11.4Hz, 10 - H)
7.90 (1H, dd $J_{12,F}$ = 10.3Hz, 12 - H)
8.37 (1H, dd $J_{9,F}$ = 5.9Hz, 9 - H)

Example 14

7 - Ethyl - 11 - chlorocamptothecin

Using 2 - amino - 4 - chloropropiophenone (see Preparative Example 2: 821 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.76 g (45.7%) of the title compound is obtained.

MP 205 - 209 °C (d)
IR (KBr): 3375, 2965, 2920, 1745, 1654, 1602, 1155.
NMR (DMSO - d_6) δppm:
0.89 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.31 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.78 - 1.96 (2H, m, 20 - CH_2CH_3)
3.22 (2H, q, 7 - CH_2CH_3)
5.30 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.51 (1H, s, 20 - OH)
7.32 (1H, s, 14 - H)
7.72 (1H, dd $J_{9,10}$ = 9.2Hz, $J_{10,12}$ = 2.2Hz, 10 - H)
8.19 (1H, d, 12 - H)
8.30 (1H, d, 9 - H)

Example 15

7 - Ethyl - 11 - bromocamptothecin

Using 2 - amino - 4 - bromopropiophenone (see Preparative Example 3: 1.02 g, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.75 g (40.5%) of the title compound is obtained.

MP 202 - 204 °C (d)
IR (KBr): 3375, 2965, 2915, 1746, 1655, 1598, 1154.
NMR (DMSO - d_6) δppm:
0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.31 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.79 - 1.94 (2H, m, 20 - CH_2CH_3)
3.21 (2H, q, 7 - CH_2CH_3)
5.30 (2H, s, 5 - CH_2 -)
5.44 (2H, s, 17 - CH_2 -)
6.52 (1H, s, 20 - OH)
7.32 (1H, s, 14 - H)
7.84 (1H, dd, $J_{9,10}$ = 9.2Hz, $J_{10,12}$ = 2.2Hz, 10 - H)
8.23 (1H, d, 9 - H)
8.36 (1H, d, 12 - H)

Example 16

7,11 - Diethylcamptothecin

Using 2 - amino - 4 - ethylpropiophenone (see Preparative Example 4: 791 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.88 g (53.8%) of the title compound is obtained.

MP 224 - 227 °C (d)

IR (KBr): 3400, 2965, 2920, 2875, 1752, 1652, 1590, 1159.

NMR (DMSO - d_6) δppm:

0.89 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.31 (3H, t, J = 7.7Hz, 11 - CH_2CH_3)
1.33 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.83 - 1.91 (2H, m, 20 - CH_2CH_3)
2.87 (2H, q, 11 - CH_2CH_3)
3.15 (2H, q, 7 - CH_2CH_3)
5.30 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.51 (1H, s, 20 - OH)
7.32 (1H, s, 14 - H)
7.61 (1H, dd, $J_{9,10}$ = 8.8Hz, $J_{10,12}$ = 1.8Hz, 10 - H)
7.97 (1H, d, 12 - H)
8.20 (1H, d, 9 - H)

Example 17

7 - Ethyl - 11 - methylthiocamptothecin

Using 2 - amino - 4 - methylthiopropiophenone (see Preparative Example 6: 873 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.92 g (53.6%) of the title compound is obtained.

MP 222 - 225.5 °C (d)

IR (KBr): 3400, 2965, 2920, 1746, 1653, 1591, 1157.

NMR (DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.30 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.81 - 1.93 (2H, m, 20 - CH_2CH_3)
2.65 (3H, s, 11 - SCH_3)
3.18 (2H, q, 7 - CH_2CH_3)
5.28 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.52 (1H, s, 20 - OH)
7.30 (1H, s, 14 - H)
7.56 (1H, dd, $J_{9,10}$ = 8.8Hz, $J_{10,12}$ = 1.8Hz, 10 - H)
7.85 (1H, d, 12 - H)
8.15 (1H, d, 9 - H)

Example 18

7 - Ethyl - 11 - dimethylaminocamptothecin

Using 2 - amino - 4 - dimethylaminopropiophenone (see Preparative Example 18: 858 mg, 4.47 mmol) and p - toluenesulfonic acid (1.2 g), the reaction followed by the after - treatment is carried out in the same manner as in Example 1, whereby 0.45 g (26.6%) of the title compound is obtained.

MP 211 - 212 °C (d)

IR(KBr): 3405, 2955, 2915, 2865, 1751, 1652, 1622, 1601, 1152.

NMR(DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)

1.29 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.80 - 1.92 (2H, m, 20 - CH_2CH_3)
3.09 (6H, s, 11 - $N(CH_3)_2$)
3.13 (2H, q, 7 - CH_2CH_3)
5.20 (2H, s, 5 - CH_2 -)
5.42 (2H, s, 17 - CH_2 -)
6.47 (1H, s, 20 - OH)
7.12 (1H, d, $J_{10,12}$ = 2.6Hz, 12 - H)
7.25 (1H, s, 14 - H)
7.38 (1H, dd, 10 - H)
8.05 (1H, d, $J_{9,10}$ = 9.5Hz, 9 - H)

Example 19

7 - Ethyl - 11 - cyanocamptothecin

Using 2 - amino - 4 - cyanopropiophenone (see Preparative Example 30: 779 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.47 g (28.9%) of the title compound is obtained.

MP 288 - 292 °C (d)
IR (KBr): 3420, 2220, 1743, 1658, 1602, 1155.
NMR (DMSO - d_6) δppm:
0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.31 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.79 - 1.96 (2H, m, 20 - CH_2CH_3)
3.29 (2H, q, 7 - CH_2CH)
5.34 (2H, s, 5 - CH_2 -)
5.44 (2H, s, 17 - CH_2 -)
6.54 (1H, s, 20 - OH)
7.37 (1H, s, 14 - H)
8.12 (1H, dd, $J_{9,10}$ = 8.8Hz, $J_{10,12}$ = 1.8Hz, 10 - H)
8.28 (1H, d, 9 - H)
8.92 (1H, d, 12 - H)

Example 20

7 - Ethyl - 11 - aminocamptothecin

Using 2,4 - diaminopropiophenone (see Preparative Example 20: 734 mg, 4.47 mmol) and p - toluenesulfonic acid (1.2 g), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.12 g (7.7%) of the title compound is obtained.

MP 276 - 279 °C (d)
IR (KBr): 3360, 2960, 2920, 1737, 1641, 1597, 1511, 1163.
NMR (DMSO - d_6) δppm:
0.86 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.27 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.81 - 1.92 (2H, m, 20 - CH_2CH_3)
3.07 (2H, q, 7 - CH_2CH_3)
5.17 (2H, s, 5 - CH_2 -)
5.41 (2H, d, J_{gem} = 3.3Hz, 17 - CH_2 -)
5.92 (2H, s, 11 - NH_2)
6.46 (1H, s, 20 - OH)
7.04 (1H, d, $J_{10,12}$ = 2.2Hz, 12 - H)
7.11 (1H, dd, 10 - H)
7.22 (1H, s, 14 - H)
7.93 (1H, d, $J_{9,10}$ = 9.2Hz, 9 - H)

Example 21

7 - Ethyl - 12 - fluorocamptothecin

Using 2 - amino - 3 - fluoropropiophenone (see Preparative Example 7: 746 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.32 g (20.3%) of the title compound is obtained.

MP 244 - 245 °C (d)

IR (KBr): 3400, 2960, 1755, 1654, 1605, 1148.

NMR (DMSO - d_6) δppm:

0.89 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.32 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.82 - 1.94 (2H, m, 20 - CH_2CH_3)
3.23 (2H, q, 7 - CH_2CH_3)
5.34 (2H, s, 5 - CH_2 -)
5.44 (2H, s, 17 - CH_2 -)
6.54 (1H, s, 20 - OH)
7.34 (1H, s, 14 - H)
7.67 - 7.72 (2H, m, 10 and 11 - H)
8.08 - 8.12 (1H, m, 9 - H)

Example 22

7 - Ethyl - 9,11 - dimethoxycamptothecin

Using 2 - amino - 4,6 - dimethoxypropiophenone (see Preparative Example 14: 934 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.70 g (39.7%) of the title compound is obtained.

MP 242 - 243 °C (d)

IR (KBr): 3380, 2970, 2920, 1752, 1653, 1619, 1596, 1453, 1267, 1237, 1207, 1160.

NMR (DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.25 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.76 - 1.96 (2H, m, 20 - CH_2CH_3)
3.12 - 3.28 (2H, m, 7 - CH_2CH_3)
3.92 (3H, s, 9 or 11 - OCH_3)
3.95 (3H, s, 9 or 11 - OCH_3)
5.10 (1H, d, J_{gem} = 18.3Hz, 5 - CH(H) -)
5.16 (1H, d, 5 - CH(H) -)
5.42 (2H, s, 17 - CH_2 -)
6.48 (1H, s, 20 - OH)
6.71 (1H, d, $J_{10,12}$ = 2.6Hz, 10 - H)
7.10 (1H, d, 12 - H)
7.23 (1H, s, 14 - H)

Example 23

7 - Ethyl - 9,11 - dihydroxycamptothecin and 7 - ethyl - 11 - hydroxy - 9 - methoxycamptothecin

7 - Ethyl - 9,11 - dimethoxycamptothecin (600 mg, 1.37 mmol) is dissolved in 120 ml of 47% hydrobromic acid and the solution is boiled under reflux for 2.5 hours under a stream of nitrogen. The mixture is concentrated under reduced pressure to dryness, and the residue is isolated and purified by column chromatography on silica gel (eluent: chloroform - methanol system) and then recrystallized from ethanol wher by the title compounds, i.e. 341 mg (60.8%) of the 9,11 - dihydroxy derivative and 10 mg (1.7%) of the 11 - hydroxy - 9 - m thoxy derivative, are obtained.

7 - Ethyl - 9,11 - dihydroxycamptothecin

MP >320 °C

IR (KBr): 3370, 3180, 2965, 1744, 1651, 1595, 1273, 1174, 1160.

NMR (DMSO - d_6) δppm:

0.87 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.30 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.78 - 1.95 (2H, m, 20 - CH_2CH_3)
3.24 - 3.40 (2H, m, 7 - CH_2CH_3)
5.20 (2H, s, 5 - CH_2 -)
5.42 (2H, s, 17 - CH_2 -)
6.49 (1H, s, 20 - OH)
6.64 (1H, br. s, 10 - H)
6.86 (1H, br. s, 12 - H)
7.22 (1H, s, 14 - H)
10.09 (1H, d, J = 3.3Hz, 9 or 11 - OH)
10.54 (1H, d, J = 3.3Hz, 9 or 11 - OH)

7 - Ethyl - 11 - hydroxy - 9 - methoxycamptothecin

IR (KBr): 3380, 2965, 1737, 1652, 1598, 1383, 1269, 1239, 1153.

NMR (DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.27 (3H, t, J = 7.3Hz, 7 - CH_2CH_3)
1.78 - 1.92 (2H, m, 20 - CH_2CH_3)
3.14 - 3.31 (2H, m, 7 - CH_2CH_3)
3.95 (3H, s, 9 - OCH_3)
5.17 (2H, s, 5 - CH_2 -)
5.42 (2H, s, 17 - CH_2 -)
6.49 (1H, s, 20 - OH)
6.68 (1H, d, $J_{10,12}$ = 2.2Hz, 10 - H)
6.97 (1H, d, 12 - H)
7.22 (1H, s, 14 - H)
10.31 (1H, br. s, 11 - OH)

Example 24

7 - Ethyl - 9,12 - dimethoxycamptothecin

Using 2 - amino - 3,6 - dimethoxypropiophenone (see Preparative Example 15: 934 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.91 g (51.6%) of the title compound is obtained.

MP 241 - 243 °C (d)

IR (KBr): 3370, 3200, 2920, 2825, 1754, 1660, 1615, 1558, 1463, 1266, 1240, 1143, 1108.

NMR (DMSO - d_6) δppm:

0.90 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.26 (3H, t, J = 7.3Hz, 7 - CH_2CH_3)
1.78 - 1.97 (2H, m, 20 - CH_2CH_3)
3.27 (2H, q, 7 - CH_2CH_3)
3.92 (3H, s, 9 or 12 - OCH_3)
3.96 (3H, s, 9 or 12 - OCH_3)
5.18 (1H, d, J_{gem} = 18.7Hz, 5 - CH(H) -)
5.23 (1H, d, 5 - CH(H) -)
5.43 (2H, s, 17 - CH_2 -)
6.54 (1H, s, 20 - OH)
7.03 (1H, d, $J_{10,11}$ = 8.8Hz, 11 - H)
7.15 (1H, d, 10 - H)

7.27 (1H, s, 14-H)

Example 25

7-Ethyl-9,12-dihydroxycamptothecin

Using 7-ethyl-9,12-dimethoxycamptothecin (1.0 g, 2.29 mmol), the reaction followed by the after-treatment is carried out in the same manner as in Example 23 whereby 720 mg (76.9%) of the title compound is obtained.

MP 259-260°C (d)

IR(KBr): 3360, 2970, 1746, 1723, 1652, 1598, 1580, 1232, 1160.

NMR (DMSO-d_6) δ ppm:

0.89 (3H, t, J=7.3Hz, 20-CH_2CH_3)
1.32 (3H, t, J=7.3Hz, 7-CH_2CH_3)
1.78-1.97 (2H, m, 20-CH_2CH_3)
3.32-3.47 (2H, m, 7-CH_2CH_3)
5.29 (2H, s, 5-CH_2-)
5.41 (1H, d, J_{gem}=16.1Hz, 17-CH(H)-)
5.45 (1H, d, 17-CH(H)-)
6.51 (1H, s, 20-OH)
6.89 (1H, dd, $J_{10,11}$=8.4Hz, $J_{11,OH}$=2.6Hz, 11-H)
6.98 (1H, dd, $J_{10,OH}$=2.2Hz, 10-H)
7.58 (1H, s, 14-H)
9.07 (1H, d, 12-OH)
9.77 (1H, d, 9-OH)

Example 26

7-Ethyl-10,11-dimethoxycamptothecin

Using 2-amino-4,5-dimethoxypropiophenone (see Preparative Example 16: 934 mg, 4.47 mmol), the reaction followed by the after-treatment is carried out in the same manner as in Example 1 whereby 0.63 g (35.9%) of the title compound is obtained.

MP 261-263°C (d)

IR(KBr): 3390, 3090, 2960, 1745, 1656, 1593, 1504, 1253, 1156.

NMR (DMSO-d_6) δppm:

0.88 (3H, t, J=7.3Hz, 20-CH_2CH_3)
1.32 (3H, t, J=7.7Hz, 7-CH_2CH_3)
1.77-1.95 (2H, m, 20-CH_2CH_3)
3.17 (2H, q, 7-CH_2CH_3)
3.97 (3H, s, 10 or 11-OCH_3)
4.00 (3H, s, 10 or 11-OCH_3)
5.25 (2H, s, 5-CH_2-)
5.42 (2H, s, 17-CH_2-)
6.39-6.55 (1H, br, 20-OH)
7.25 (1H, s, 14-H)
7.43 (1H, s, 9 or 12-H)
7.53 (1H, s, 9 or 12-H)

Example 27

7-Ethyl-10,11-dihydroxycamptothecin and 7-ethyl-10-hydroxy-11-methoxycamptothecin

Using 7-ethyl-10,11-dimethoxycamptothecin (1.0 g, 2.29 mmol), the reaction followed by the after-treatment is carried out in the same manner as in Example 23 whereby the title compounds, 356 mg (38.0%) of the 10,11-dihydroxy derivative and 38 mg (3.9%) of the 10-hydroxy-11-methoxy derivative, are obtained.

7 - Ethyl - 10,11 - dihydroxycamptothecin

MP >320° C
IR (KBr): 3400, 2965, 1737, 1647, 1588, 1552, 1465, 1263, 1162.
NMR (DMSO - d_6) δ ppm:
0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.29 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.78 - 1.94 (2H, m, 20 - CH_2CH_3)
3.05 (2H, q, 7 - CH_2CH_3)
5.22 (2H, s, 5 - CH_2 -)
5.41 (2H, s, 17 - CH_2 -)
6.20 - 6.76 (1H, br, 20 - OH)
7.22 (1H, s, 14 - H)
7.38 (1H, s, 9 or 12 - H)
7.39 (1H, s, 9 or 12 - H)
10.13 (1H, br.s, 10 or 11 - OH)
10.38 (1H, br.s, 10 or 11 - OH)

7 - Ethyl - 10 - hydroxy - 11 - methoxycamptothecin

MP 207 - 210° C (d)
IR (KBr): 3520, 3400, 2910, 1734, 1653, 1603, 1505, 1260, 1156.
NMR (DMSO - d_6) δppm:
0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.29 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.78 - 1.93 (2H, m, 20 - CH_2CH_3)
3.07 (2H, q, 7 - CH_2CH_3)
3.99 (3H, s, 11 - OCH_3)
5.25 (2H, s, 5 - CH_2 -)
5.39 (1H, d, J_{gem} = 16.1Hz, 17 - CH(H) -)
5.44 (1H, d, 17 - CH(H) -)
6.51 (1H, s, 20 - OH)
7.26 (1H, s, 14 - H)
7.42 (1H, s, 9 - H)
7.53 (1H, s, 12 - H)
10.23 (1H, br. s, 10 - OH)

Example 28

7 - Ethyl - 10,11 - dichlorocamptothecin

Using 2 - amino - 4,5 - dichloropropiophenone (see Preparative Example 13: 975 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.72 g (40.0%) of the title compound is obtained.

MP 258 - 262° C (d)
IR (KBr): 3330, 3090, 2960, 2910, 1744, 1660, 1612, 1463, 1159.
NMR (DMSO - d_6) δppm:
0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.29 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.78 - 1.97 (2H, m, 20 - CH_2CH_3)
3.22 (2H, q, 7 - CH_2CH_3)
5.31 (2H, s, 5 - CH_2 -)
5.44 (2H, s, 17 - CH_2 -)
6.53 (1H, s, 20 - OH)
7.31 (1H, s, 14 - H)
8.42 (1H, s, 9 or 12 - H)
8.54 (1H, s, 9 or 12 - H)

Example 29

7 - Ethyl - 9,10,11 - trimethoxycamptothecin

Using 2 - amino - 4,5,6 - trimethoxypropiophenone (see Preparative Example 17: 1.07 g, 4,47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.95 g (50.5%) of the title compound is obtained.

MP 221 - 223 °C (d)

IR(KBr): 3385, 2910, 1748, 1654, 1605, 1467, 1415, 1265, 1241, 1155, 1095, 1038.

NMR(DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.30 (3H, t, J = 7.3Hz, 7 - CH_2CH_3)
1.77 - 1.98 (2H, m, 20 - CH_2CH_3)
3.18 - 3.33 (2H, m, 7 - CH_2CH_3)
3.90 (3H, s, 9, 10 or 11 - OCH_3)
3.99 (3H, s, 9, 10 or 11 - OCH_3)
4.00 (3H, s, 9, 10 or 11 - OCH_3)
5.26 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.48 (1H, s, 20 - OH)
7.26 (1H, s, 14 - H)
7.44 (1H, s, 12 - H)

Example 30

7 - Propyl - 10 - methylcamptothecin

Using 2 - amino - 5 - methylbutyrophenone (see Preparative Example 25: 792 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 1.02 g (62.1%) of the title compound is obtained.

MP 206 - 208 °C (d)

IR(KBr): 3345, 2950, 2920, 2870, 1748, 1653, 1590, 1552, 1462, 1156.

NMR(DMSO - d_6) δppm:

0.89 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.05 (3H, t, J = 7.3Hz, 7 - $CH_2CH_2CH_3$)
1.72 (2H, tq, J = 7.3Hz, 7 - $CH_2CH_2CH_3$)
1.78 - 1.95 (2H, m, 20 - CH_2CH_3)
2.56 (3H, s, 10 - CH_3)
3.21 (2H, t, J = 7.3Hz, 7 - $CH_2CH_2CH_3$)
5.20 (2H, s, 5 - CH_2 -)
5.40 (1H, d, J_{gem} = 16.5Hz, 17 - CH(H) -)
5.44 (1H, d, J_{gem} = 16.5Hz, 17 - CH(H) -)
6.50 (1H, br.s, 20 - OH)
7.29 (1H, s, 14 - H)
7.56 (1H, dd, $J_{9,11}$ = 1.5Hz, $J_{11,12}$ = 8.8Hz, 11 - H)
7.98 (1H, d, 9 - H)
8.02 (1H, d, 12 - H)

Example 31

7 - Propyl - 11 - chlorocamptothecin

Using 2 - amino - 4 - chlorobutyrophenone (see Preparative Example 24: 803 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.75 g (45.5%) of th titl compound is obtained.

MP 150 - 156 °C (d)

IR(KBr): 3400, 2955, 2920, 1748, 1655, 1604, 1155.

NMR(DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.04 (3H, t, J = 7.3Hz, 7 - $CH_2CH_2CH_3$)
1.73 (2H, tq, J = 7.3Hz, 7 - $CH_2CH_2CH_3$)
1.78 - 1.95 (2H, m, 20 - CH_2CH_3)
3.18 (2H, t, J = 7.3Hz, 7 - $CH_2CH_2CH_3$)
5.30 (2H, s, 5 - CH_2 -)
5.44 (2H, s, 17 - CH_2 -)
6.52 (1H, s, 20 - OH)
7.33 (1H, s, 14 - H)
7.73 (1H, dd, $J_{9,10}$ = 8.8Hz, $J_{10,11}$ = 2.2Hz, 10 - H)
8.20 (1H, d, 12 - H)
8.32 (1H, d, 9 - H)

Example 32

7 - Butyl - 10 - bromocamptothecin

Using 2 - amino - 5 - bromovalerophenone (see Preparative Example 28: 1.14 g, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.73 g (37.4%) of the title compound is obtained.

MP 223 - 229 °C (d)
IR(KBr): 3350, 2945, 1745, 1654, 1598, 1456, 1161.
NMR(DMSO - d_6) δppm:

0.89 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
0.96 (3H, t, J = 7.3Hz, 7 - $CH_2CH_2CH_2CH_3$)
1.49 (2H, tq, J = 7.3Hz, 7 - $CH_2CH_2CH_2CH_3$)
1.58 - 1.70 (2H, m, 7 - $CH_2CH_2CH_2CH_3$)
1.78 - 1.96 (2H, m, 20 - CH_2CH_3)
3.16 (2H, t, J = 8.1Hz, 7 - $CH_2CH_2CH_2CH_3$)
5.26 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.51 (1H, s, 20 - OH)
7.31 (1H, s, 14 - H)
7.93 (1H, dd, $J_{9,11}$ = 2.2Hz, $J_{11,12}$ = 9.2Hz, 11 - H)
8.06 (1H, d, 12 - H)
8.40 (1H, d, 9 - H)

Example 33

7 - Isopropyl - 12 - bromocamptothecin

Using 2 - amino - 3 - bromoisobutyrophenone (see Preparative Example 26: 1.08 g, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 0.32 g (17.1%) of the title compound is obtained.

MP 268 - 272 °C (d)
IR(KBr): 3500, 2965, 1727, 1655, 1606, 1553, 1152.
NMR(DMSO - d_6) δppm:

0.90 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.49 (6H, d, J = 5.9Hz, 7 - $CH(CH_3)_2$)
1.78 - 1.98 (2H, m, 20 - CH_2CH_3)
3.96 - 4.12 (1Hm, m, 7 - $CH(CH_3)_2$)
5.44 (4H, s, 5 and 17 - CH_2 -)
6.57 (1H, s, 20 - OH)
7.37 (1H, s, 14 - H)
7.60 (1H, dd, J = 8.1Hz, 10 - H)
8.23 (1H, d, J = 7.3Hz, 9 or 10 - H)
8.42 (1H, d, J = 8.8Hz, 9 or 10 - H)

Example 34

7 - Ethyl - 11 - fluoro - 10 - m thoxycamptothecin

Using 2 - amino - 4 - fluoro - 5 - methoxypropiophenone (see Preparative Example 33: 882 mg, 4,47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 1 whereby 1.00 g (57.8%) of the title compound is obtained. It was recrystallized from chloroform - n - hexane. Colorless crystals.

MP 242 - 244 °C (d)

IR(KBr)cm^{-1}: 3400, 1744, 1656, 1606, 1511, 1263, 1156.

NMR(DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - $CH_2\underline{CH_3}$)
1.32 (3H, t, J = 7.7Hz, 7 - $CH_2\underline{CH_3}$)
1.75 - 1.97 (2H, m, 20 - $CH_2\underline{CH_3}$)
3.22 (2H, q, 7 - CH_2CH_3)
4.08 (3H, s, - $O\underline{CH_3}$)
5.29 (2H, s, 5 - H_2)
5.43 (2H, s, 17 - H_2)
6.50 (1H, s, 20 - OH)
7.27 (1H, s, 14 - H)
7.65 (1H, d, $J_{9,F}$ = 9.2Hz, 9 - H)
7.95 (1H, d, $J_{12,F}$ = 12.5Hz, 12 - H)

Example 35

7 - Ethyl - 11 - fluoro - 10 - hydroxycamptothecin

Using 7 - ethyl - 11 - fluoro - 10 - methoxycamptothecin (1.7 g, 4.00 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Example 23 whereby 1.39 g (84.5%) of the title compound is obtained.

MP 225 - 228 °C (d)

NMR(DMSO - d_6) δ ppm:

0.87 (3H, t, J = 7.3Hz, 20 - $CH_2\underline{CH_3}$)
1.30 (3H, t, J = 7.7Hz, 7 - $CH_2\underline{CH_3}$)
1.76 - 1.95 (2H, m, 20 - $CH_2\underline{CH_3}$)
3.09 (2H, q, 7 - CH_2CH_3)
5.28 (2H, s, 5 - $\underline{H_2}$)
5.42 (2H, s, 17 - H_2)
7.26 (1H, s, 14 - H)
7.60 (1H, d, $J_{9,F}$ = 9.5Hz, 9 - H)
7.91 (1H, d, $J_{12,F}$ = 12.1Hz, 12 - H)
10.64 - 11.10 (1H, br, 10 - OH)

Referential Example 1

7 - Methyl - 10 - ethoxycamptothecin

1,5 - Dioxo(5' - ethyl - 2'H,5'H,6'H - 6 - oxopyrano) [3',4' - f] - Δ6(8) - tetrahydroindolidine (1.00 g, 4.06 mmol), 2 - amino - 5 - ethoxyacetophenone (800 mg, 4,47 mmol) and p - toluenesulfonic acid (320 mg) are dissolved in 200 ml of toluene and the solution is boiled under reflux for 24 hours using a Dean - Stark apparatus. The solvent is distilled off under reduced pressure and the residue is washed with chloroform - ether and then dissolved in 240 ml of dimethylformamide. 2.37 g of cupric chloride and 0.71 ml of 40% aqueous solution of dimethylamine are added to the solution, and oxygen gas is then blown into the mixture until the starting materials are no longer observed on the thin layer chromatogram. After completion of the reaction, th solv nts are distilled off under reduced pressure, and the residu is subjected to isolation and purification by column chromatography on silica gel (chloroform - methanol system) wh r by 0.58 g (58.3%) of the titl compound, yellow in color, is obtained.

MP 243 - 244 °C (d - decomposition)
IR(KBr): 3400, 2970, 2920, 1740, 1657, 1599, 1236, 1158.
NMR(DMSO - d_6) δppm:
0.89 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.43 (3H, t, J = 7.0Hz, 10 - OCH_2CH_3)
1.81 - 1.92 (2H, m, 20 - CH_2CH_3)
2.71 (3H, s, 7 - CH_3)
4.25 (2H, q, 10 - OCH_2CH_3)
5.23 (2H, s, 5 - CH_2 -)
5.42 (2H, s, 17 - CH_2 -)
6.48 (1H, s, 20 - OH)
7.26 (1H, s, 14 - H)
7.42 (1H, d, $J_{9,11}$ = 2.9Hz, 9 - H)
7.48 (1H, dd, 11 - H)
8.04 (1H, d, $J_{11,12}$ = 9.2Hz, 12 - H)

Referential Example 2

7 - Ethyl - 10 - methylthiocamptothecin

Using 2 - amino - 5 - methylthiopropiophenone (see Preparative Example 12: 873 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Referential Example 1 whereby 1.07 g (62.6%) of the title compound is obtained.

MP 259 - 261 °C (d)
IR(KBr): 3350, 2970, 2910, 1740, 1652, 1593, 1162.
NMR(DMSO - d_6) δppm:
0.93 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.38 (3H, t, J = 8.1Hz, 7 - CH_2CH_3)
1.83 - 1.94 (2H, m, 20 - CH_2CH_3)
2.67 (3H, s, 10 - SCH_3)
3.22 (2H, q, 7 - CH_2CH_3)
5.28 (2H, s, 5 - CH_2 -)
5.34 (1H, d, J_{gem} = 16.3Hz, 17 - CH(H) -)
5.49 (1H, d, 17 - CH(H) -)
6.40 (1H, s, 20 - OH)
7.38 (1H, s, 14 - H)
7.68 (1H, dd, $J_{9,11}$ = 1.5Hz, $J_{11,12}$ = 8.8Hz, 11 - H)
7.83 (1H, d, 9 - H)
8.06 (1H, d, 12 - H)

Referential Example 3

7 - Ethyl - 11 - methoxycamptothecin

Using 2 - amino - 4 - methoxypropiophenone (see Preparative Example 5: 802 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Referential Example 1 whereby 1.01 g (61.4%) of the title compound is obtained.

MP 228 - 230 °C (d)
IR(KBr): 3375, 2965, 2920, 1746, 1654, 1605, 1224, 1156.
NMR(DMSO - d_6) δppm:
0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.30 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.78 - 1.96 (2H, m, 20 - CH_2CH_3)
3.18 (2H, q, 7 - CH_2CH_3)
3.96 (3H, s, 11 - OCH_3)
5.26 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.49 (1H, s, 20 - OH)

7.30 (1H, s, 14 - H)
7.35 (1H, dd, $J_{9,10}$ = 9.2Hz, $J_{10,11}$ = 2.6Hz, 10 - H)
7.55 (1H, d, 12 - H)
8.17 (1H, d, 9 - H)

Referential Example 4

7 - Methyl - 10 - hydroxycamptothecin

7 - Methyl - 10 - ethoxycamptothecin (2.0 g, 4.92 mmol) is dissolved, with heating, in 700 ml of 1,1,2,2 - tetrachloroethane, and aluminum chloride (1.97 g, 14.8 mmol) is then added to the solution. The mixture is boiled under reflux with stirring for 24 hours. The reaction mixture is concentrated under reduced pressure to dryness, and the residue is subjected to isolation and purification by column chromatography on silica gel (eluent: chloroform - methanol system) and then recrystallized from methanol whereby 0.50 g (26.9%) of the title compound is obtained as yellow prisms.

MP 341 - 345.5 °C (d)
IR(KBr): 3395, 1731, 1652, 1591, 1526.
NMR(DMSO - d_6) δppm:
0.88 (3H, t, J = 7.0Hz, 20 - CH_2CH_3)
1.81 - 1.92 (2H, m, 20 - CH_2CH_3)
2.65 (3H, s, 7 - CH_3)
5.24 (2H, s, 5 - CH_2 -)
5.41 (2H, s, 17 - CH_2 -)
6.46 (1H, s, 20 - OH)
7.24 (1H, s, 14 - H)
7.35 (1H, d, $J_{9,11}$ = 2.6Hz, 9 - H)
7.41 (1H, dd, 11 - H)
8.01 (1H, d, $J_{11,12}$ = 9.2Hz, 12 - H)
10.29 (1H, br. s, 10 - OH)

Referential Example 5

7 - Ethyl - 11 - hydroxycamptothecin

7 - Ethyl - 11 - methoxycamptothecin (3.0 g, 7.38 mmol) is dissolved in 120 ml of 47% hydrobromic acid and the solution is boiled under reflux for 2.5 hours under a stream of nitrogen. The mixture is concentrated under reduced pressure to dryness, and the residue is isolated and purified by column chromatography on silica gel (eluent: chloroform - methanol system) and recrystallized from ethanol whereby 2.16 g (74.7%) of the title compound is obtained as yellow crystals.

MP >320 °C
IR(KBr): 3500, 3100, 2965, 1741, 1725, 1653, 1590, 1567, 1463, 1256, 1230, 1157, 1143.
NMR(DMSO - d_6) δppm:
0.89 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.29 (3H, t, J = 7.7Hz, 7 - CH_2CH_3)
1.78 - 1.95 (2H, m, 20 - CH_2CH_3)
3.14 (2H, q, 7 - CH_2CH_3)
5.23 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.49 (1H, s, 20 - OH)
7.26 (1H, dd, $J_{9,10}$ = 9.2Hz, $J_{10,11}$ = 2.2Hz, 10 - H)
7.27 (1H, s, 14 - H)
7.37 (1H, d, 12 - H)
8.11 (1H, d, 9 - H)
10.35 (1H, s, 11 - OH)

Referential Example 6

7 - Isopropyl - 9 - methoxycamptothecin

Using 2 - amino - 6 - methoxyisobutyrophenone (861 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Referential Example 1 whereby 0.80 g (46.9%) of the title compound is obtained.

MP 234 - 237° C (d)

IR(KBr): 3500, 3330, 2950, 1751, 1735, 1665, 1616, 1593, 1568, 1460, 1250, 1232, 1157.

NMR(DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.43 (3H, d, J = 7.0Hz, 7 - $CH(CH_3)CH_3$)
1.44 (3H, d, J = 7.0Hz, 7 - $CH(CH_3)CH_3$)
1.78 - 1.95 (2H, m, 20 - CH_2CH_3)
4.00 (3H, s, 9 - OCH_3)
4.69 - 5.15 (1H, m, 7 - $CH(CH_3)_2$)
5.39 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.50 (1H, s, 20 - OH)
7.18 (1H, dd, J = 5.1, 4.0Hz, 11 - H)
7.29 (1H, s, 14 - H)
7.70 - 7.75 (2H, m, 10 and 12 - H)

Referential Example 7

7 - Isopropyl - 9 - hydroxycamptothecin

Using 7 - isopropyl - 9 - methoxycamptothecin (1.3 g, 3.09 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Referential Example 5 whereby 796 mg (63.3%) of the title compound is obtained.

MP 214 - 218° C (d)

IR(KBr): 3265, 2965, 1743, 1653, 1594, 1569, 1286, 1156.

NMR(DMSO - d_6) δ ppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.42 (3H, br. d, 7 - $CH(CH_3)CH_3$)
1.43 (3H, br. d, 7 - $CH(CH_3)CH_3$)
1.78 - 1.95 (2H, m, 20 - CH_2CH_3)
5.10 - 5.26 (1H, m, 7 - $CH(CH_3)_2$)
5.40 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.50 (1H, s, 20 - OH)
7.06 (1H, dd, J = 6.2, 2.9Hz, 11 - H)
7.29 (1H, s, 14 - H)
7.57 - 7.63 (2H, m, 10 and 12 - H)
10.63 (1H, s, 9 - OH)

Referential Example 8

7 - Isopropyl - 11 - methoxycamptothecin

Using 2 - amino - 4 - methoxyisobutyrophenone (861 mg, 4.47 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Referential Example 1 whereby 0.54 g (31.5%) of the title compound is obtained.

MP 195 - 196° C (d)

IR(KBr): 3420, 2965, 1739, 1657, 1622, 1598, 1224, 1154.

NMR(DMSO - d_6) δppm:

0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)

1.46 (3H, d, J = 7.0Hz, 7 - CH(CH_3)CH_3)
1.47 (3H, d, J = 7.0Hz, 7 - CH(CH_3)CH_3)
1.77 - 1.95 (2H, m, 20 - CH_2CH_3)
3.90 - 4.04 (1H, m, 7 - $CH(CH_3)_2$)
3.96 (3H, s, 11 - OCH_3)
5.38 (2H, s, 5 - CH_2 -)
5.43 (2H, s, 17 - CH_2 -)
6.50 (1H, s, 20 - OH)
7.31 (1H, s, 14 - H)
7.35 (1H, dd, $J_{9,10}$ = 9.5Hz, $J_{10,12}$ = 2.9Hz, 10 - H)
7.56 (1H, d, 12 - 0H)
8.30 (1H, d, 9 - H)

Referential Example 9

7 - Isopropyl - 11 - hydroxycamptothecin

Using 7 - isopropyl - 11 - methoxycamptothecin (1.0 g, 2.38 mmol), the reaction followed by the after - treatment is carried out in the same manner as in Referential Example 5 whereby 749 mg (77.5%) of the title compound is obtained.

MP >320 °C
IR(KBr): 3420, 3100, 2970, 1739, 1652, 1618, 1590, 1566, 1245, 1230, 1154.
NMR(DMSO - d_6) δ ppm:
0.88 (3H, t, J = 7.3Hz, 20 - CH_2CH_3)
1.45 (3H, d, J = 7.0Hz, 7 - CH(CH_3)CH_3)
1.46 (3H, d, J = 7.0Hz, 7 - CH(CH_3)CH_3)
1.57 - 1.95 (2H, m, 20 - CH_2CH_3)
3.87 - 4.02 (1H, m, 7 - $CH(CH_3)_2$)
5.34 (2H, s, 5 - CH_2 -)
5.42 (2H, s, 17 - CH_2 -)
6.00 - 6.95 (1H, br, 20 - OH)
7.26 (1H, dd, $J_{9,10}$ = 9.2Hz, $J_{10,12}$ = 2.6Hz, 10 - H)
7.28 (1H, s, 14 - H)
7.37 (1H, d, 12 - H)
8.24 (1H, d, 9 - H)
10.38 (1H, br. s, 11 - OH)

Preparative Examples where the compounds used in each of the Examples described above are prepared are shown below.

Preparative Example 1

2 - Amino - 4 - fluoropropiophenone

25.0 g (0.21 mol) of boron trichloride is added to 100 ml of dry benzene with ice cooling and stirring, and a solution of 21.3g (0.19 mol) of 3 - fluoroaniline in 200 ml of dry benzene is added to the mixture under a stream of nitrogen. 21.1 g (0.38 mol) of propionitrile and 28.4 g (0.21 mol) of aluminum chloride (ground in a mortar) are added in that order, and the mixture is boiled under reflux for 8 hours. After ice - cooling, 200 - 220 ml of 2N hydrochloric acid is carefully added, and the mixture is stirred at 80 °C for 1 hour. After cooling, 200 ml of water is added and the mixture is extracted 2 - 3 times with benzene. The benzene layer is separated, washed with water, dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue obtained is isolated and purified by column chromatography on silica gel (eluent: toluene - ethyl acetate system) and recrystallized from ether - n - hexane whereby 19.98 g (62.2%) of the title compound is obtained.

MP 58 - 61 °C
IR(KBr): 3420, 3310, 1646, 1620, 1587, 1555, 1435, 1207, 1179, 1128.
NMR($CDCl_3$) δ ppm:
1.20 (3H, t, J = 7.3Hz, - CH_2CH_3)
2.93 (2H, q, - CH_2CH_3)

6.30 (1H, dd, $J_{3,5}$ = 2.6Hz, $J_{3,F}$ = 11.0Hz, 3 - H)
6.34 (1H, ddd, $J_{5,6}$ = 8.8Hz, $J_{5,F}$ = 10.6Hz, 5 - H)
6.45 (2H, br. s, - NH)
7.74 (1H, dd, $J_{6,F}$ = 6.2Hz, 6 - H)

Preparative Example 2

2 - Amino - 4 - chloropropiophenone

Using 24.5 g (0.19 mol) of 3 - chloroaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 15.73 g (44.6%) of the title compound is obtained.

MP 73 - 75 °C
IR(KBr): 3480, 3445, 3350, 1651, 1638, 1613, 1531, 1200.
NMR($CDCl_3$) δ ppm:

1.19 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.93 (2H, q, $-\underline{CH_2}CH_3$)
6.37 (2H, br.s, $-\overline{NH_2}$)
6.59 (1H, dd, $J_{3,5}$ = 2.2Hz, $J_{5,6}$ = 8.8Hz, 5 - H)
6.46 (1H, d, 3 - H)
7.65 (1H, d, 6 - H)

Preparative Example 3

2 - Amino - 4 - bromopropiophenone

Using 33.0 g (0.19 mol) of 3 - bromoaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 20.15 g (46.0%) of the title compound is obtained.

MP 86 - 88 °C
IR(KBr): 3490, 3440, 3350, 3320, 1652, 1638, 1609, 1597, 1529, 1209.
NMR($CDCl_3$) δppm:

1.19 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.93 (2H, q, $-\underline{CH_2}CH_3$)
6.33 (2H, br.s, $-\overline{NH_2}$)
6.75 (1H, dd, $J_{3,5}$ = 1.8Hz, $J_{5,6}$ = 8.4Hz, 5 - H)
6.83 (1H, d, 3 - H)
7.58 (1H, d, 6 - H)

Preparative Example 4

2 - Amino - 4 - ethylpropiophenone

Using 23.2 g (0.19 mol) of 3 - ethylaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 21.10 g (66.7%) of the title compound is obtained.

IR(neat): 3440, 3325, 2960, 2920, 1635, 1615, 1576, 1212.
NMR($CDCl_3$) δppm:

1.20 (3H, t, J = 7.3Hz, 4 - $CH_2\underline{CH_3}$)
1.21 (3H, t, J = 7.3Hz, - $COCH_2\underline{CH_3}$)
2.55 (2H, q, 4 - $\underline{CH_2}CH_3$)
2.94 (2H, q, - $CO\underline{CH_2}CH_3$)
6.1 - 6.4 (2H, br. s, $-\overline{NH_2}$)
6.47 (1H, d, $J_{3,5}$ = 2.2Hz, 3 - H)
6.49 (1H, dd, 5 - H)
7.66 (1H, d. $J_{5,6}$ = 8.1Hz, 6 - H)

Preparative Example 5

2 - Amino - 4 - methoxypropiophenone

Using 23.7 g (0.19 mol) of 3 - methoxyaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 20.30 g (59.0%) of the title compound is obtained.

MP 54 - 56 °C

IR(KBr): 3435, 3320, 1640, 1626, 1602, 1583, 1533, 1456, 1370, 1205, 1142.

NMR($CDCl_3$) δ ppm:

1.19 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.90 (2H, q, $-\underline{CH_2}CH_3$)
3.79 (3H, s, $-O\overline{CH_3}$)
6.07 (1H, d, $J_{3,5}$ = 2.6Hz, 3 - H)
6.22 (1H, dd, 5 - H)
6.41 (2H, br.s, $-NH_2$)
7.67 (1H, d, $J_{5,6}$ = 8.8Hz, 6 - H)

Preparative Example 6

2 - Amino - 4 - methylthiopropiophenone

Using 26.7 g (0.19 mol) of 3 - methylthioaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 wherein 28.30 g (76.3%) of the title compound is obtained.

MP 75 - 76.5 °C

IR(KBr): 3440, 3400, 3300, 2960, 2910, 1642, 1623, 1598, 1573, 1211.

NMR($CDCl_3$) δ ppm:

1.20 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.46 (3H, s, $-SCH_3$)
2.92 (2H, q, $-\underline{CH_2}CH_3$)
6.0 - 6.8 (2H, br.s, $-NH_2$)
6.42 (1H, d, $J_{3,5}$ = 1.5Hz, 3 - H)
6.50 (1H, dd, 5 - H)
7.63 (1H, d, $J_{5,6}$ = 8.1Hz, 6 - H)

Preparative Example 7

2 - Amino - 3 - fluoropropiophenone

Using 21.3 g (0.19 mol) of 2 - fluoroaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 wherein 0.82 g(2.8%) of the title compound is obtained.

MP 40 - 42 °C

IR(KBr): 3420, 3310, 2970, 2920, 1644, 1625, 1452, 1219.

NMR($CDCl_3$) δ ppm:

1.21 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.98 (2H, q, $-\underline{CH_2}CH_3$)
5.6 - 6.6 (2H, br.s, $-NH_2$)
6.56 (1H, m, 5 - H)
7.10 (1H, m, 4 - H)
7.54 (1H, m, 6 - H)

Preparative Example 8

2 - Amino - 5 - fluoropropiophenone

Using 21.3 g (0.19 mol) of 4 - fluoroaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 wherein 7.00 g (21.8%) of the title compound is obtained.

MP 70 - 72 ° C
IR(KBr): 3420, 3325, 1636, 1593, 1558, 1483, 1227, 1171.
NMR($CDCl_3$) δppm:
1.21 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.93 (2H, q, $-\underline{CH_2}CH_3$)
6.11 (2H, br. s, $-NH_2$)
6.61 (1H, dd, $J_{3,4}$ = 9.2Hz, $J_{3,F}$ = 4.8Hz, 3 - H)
7.03 (1H, ddd, $J_{4,6}$ = 2.9Hz, $J_{4,F}$ = 10.6Hz, 4 - H)
7.41 (1H, dd, $J_{6,F}$ = 9.9Hz, 6 - H)

Preparative Example 9

2 - Amino - 5 - chloropropiophenone

Using 24.5 g (0.19 mol) of 4 - chloroaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 wherein 3.62 g (10.3%) of the title compound is obtained.
MP 76 - 78 ° C
IR(KBr): 3430, 3330, 1636, 1618, 1545, 1202.
NMR($CDCl_3$) δ ppm:
1.20 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.94 (2H, q, $-\underline{CH_2}CH_3$)
6.27 (2H, br.s, $-NH_2$)
6.60 (1H, d, $J_{3,4}$ = 8.8Hz, 3 - H)
7.19 (1H, dd, $J_{4,6}$ = 2.6Hz, 4 - H)
7.69 (1H, d, 6 - H)

Preparative Example 10

2 - Amino - 5 - bromopropiophenone

Using 33.0 g (0.19 mol) of 4 - bromoaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 3.85 g (8.8%) of the title compound is obtained.
MP 78 - 79 ° C
IR(KBr): 3430, 3320, 1645, 1621, 1208.
NMR($CDCl_3$) δppm:
1.20 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.94 (2H, q, $-\underline{CH_2}CH_3$)
6.28 (2H, br.s, $-NH_2$)
6.56 (1H, d, $J_{3,4}$ = 8.8Hz, 3 - H)
7.31 (1H, dd, $J_{4,6}$ = 2.2Hz, 4 - H)
7.84 (1H, d, 6 - H)

Preparative Example 11

2 - Amino - 5 - methylpropiophenone

Using 20.6 g (0.19 mol) of 4 - methylaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 wherein 12.44 g (40.2%) of the title compound is obtained.
MP 75.5 - 76.5 ° C
IR(KBr): 3430, 3315, 2965, 2900, 1635, 1587, 1553, 1226, 1193.
NMR($CDCl_3$) δ ppm:
1.20 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.26 (3H, s, $-CH_3$)
2.97 (2H, q, $-\underline{CH_2}CH_3$)
5.9 - 6.4 (2H, br. s, $-NH_2$)
6.59 (1H, d, $J_{3,4}$ = 8.1Hz, 3 - H)
7.09 (1H, dd, 4 - H)
7.53 (1H, d, $J_{4,6}$ = 1.5Hz, 6 - H)

Preparative Exampl 12

2 - Amino - 5 - methylthiopropiophenone

Using 26.7 g (0.19 mol) of 4 - methylthioaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 20.60 g (55.6%) of the title compound is obtained.

MP 64.5 - 65.5 °C

IR(KBr): 3430, 3315, 2965, 2900, 1635, 1618, 1578, 1540, 1205, 1158.

NMR($CDCl_3$) δ ppm:

1.21 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.42 (3H, s, $-SCH_3$)
2.98 (2H, q, $-\underline{CH_2}CH_3$)
6.1 - 6.6 (2H, br.s, $-NH_2$)
6.63 (1H, d, $J_{3,4}$ = 8.1Hz, 3 - H)
7.32 (1H, dd, 4 - H)
7.82 (1H, d, $J_{4,6}$ = 2.2Hz, 6 - H)

Preparative Example 13

2 - Amino - 4,5 - dichloropropiophenone

Using 31.1 g (0.19 mol) of 3,4 - dichloroaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 1.63 g (3.9%) of the title compound is obtained.

MP 88 - 89 °C

IR(KBr): 3420, 3325, 1648, 1609, 1577, 1521, 1457, 1204.

NMR($CDCl_3$) δ ppm:

1.20 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.93 (2H, q, $-\underline{CH_2}CH_3$)
6.30 (2H, br.s, $-\overline{N}H_2$)
6.78 (1H, s, 3 - H)
7.79 (1H, s, 6 - H)

Preparative Example 14

2 - Amino - 4,6 - dimethyoxypropiophenone

Using 29.4 g (0.19 mol) of 3,5 - dimethoxyaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 36.76 g (91.5%) of the title compound is obtained.

MP 63 - 66 °C

IR(KBr): 3420, 3300, 2970, 2915, 1608, 1570, 1205, 1161, 1140.

NMR($CDCl_3$) δppm:

1.12 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.91 (2H, q, $-\underline{CH_2}CH_3$)
3.77 (3H, s, 4 or $\overline{6}-OCH_3$)
3.81 (3H, s, 4 or 6 - OCH_3)
5.72 (1H, d, $J_{3,5}$ = 2.2Hz, 3 - H)
5.77 (1H, d, 5 - H)
6.24 (2H, br. s, $-NH_2$)

Preparative Example 15

2 - Amino - 3,6 - dimethoxypropiophenone

Using 29.4 g (0.19 mol) of 2,5 - dimethoxyanilin , the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 2.46 g (6.1%) of the titl compound is

obtained as an oil.

IR(neat): 3470, 3345, 2930, 2818, 1628, 1608, 1538, 1471, 1353, 1259, 1224, 1108.

NMR($CDCl_3$) δ ppm:

1.14 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.95 (2H, q, $-\underline{CH_2}CH_3$)
3.77 (3H, s, 3 or $\overline{6}-OCH_3$)
3.78 (3H, s, 3 or 6 - OCH_3)
6.05 (1H, d, $J_{4,5}$ = 8.8Hz, 5 - H)
6.07 (2H, br.s, $-NH_2$)
6.70 (1H, d, 4 - H)

Preparative Example 16

2 - Amino - 4,5 - dimethoxypropiophenone

Using 29.4 g (0.19 mol) of 3,4 - dimethoxyaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 24.27 g (60.4%) of the title compound is obtained.

MP 128 - 129 °C

IR(KBr): 3420, 3320, 1627, 1589, 1539, 1506, 1449, 1394, 1231, 1198, 1152.

NMR($CDCl_3$) δppm:

1.21 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.90 (2H, q, $-\underline{CH_2}CH_3$)
3.83 (3H, s, 4 or $\overline{5}-OCH_3$)
3.87 (3H, s, 4 or 5 - OCH_3)
5.6 - 6.9 (2H, br, $-NH_2$)
6.11 (1H, s, 3 - H)
7.16 (1H, s, 6 - H)

Preparative Example 17

2 - Amino - 4,5,6 - trimethoxypropiophenone

Using 35.2 g (0.19 mol) of 3,4,5 - trimethoxyaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 wherein 6.52 g (14.2%) of the title compound is obtained.

MP 75 - 77 °C

IR(KBr): 3460, 3310, 2970, 2910, 1635, 1610, 1571, 1543, 1449, 1242, 1199, 1121.

NMR($CDCl_3$) δ ppm:

1.15 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.94 (2H, q, $-\underline{CH_2}CH_3$)
3.76 (3H, s, 4, $\overline{5}$ or 6 - OCH_3)
3.83 (3H, s, 4, 5 or 6 - OCH_3)
3.93 (3H, s, 4, 5 or 6 - OCH_3)
5.84 (2H, br.s, $-NH_2$)
5.89 (1H, s, 3 - H)

Preparative Example 18

2 - Amino - 4 - dimethylaminopropiophenone

Using 35.0 g (0.19 mol) of 3 - dimethylaminoaniline hydrochloride, the reaction is carried out in the same manner as in Preparative Example 1. After completion of the reaction, the aqueous layer is made alkaline with an aqueous sodium hydroxide solution and extracted with benzene or ethyl acetate. The after - treatment is carried out in th same manner whereby 5.45 g (11.9%) of the title compound is obtained.

MP 106 - 107.5 °C

IR(KBr): 3400, 3300, 2955, 2910, 1605, 1512, 1382, 1242, 1156.

NMR($CDCl_3$) δppm:

1.19 (3H, t, J = 7.3Hz, $-CH_2CH_3$)
2.86 (2H, q, $-CH_2CH_3$)
3.00 (6H, s, $-N(CH_3)_2$)
5.76 (1H, d, $J_{3,5}$ = 2.2Hz, 3 - H)
6.07 (1H, dd, 5 - H)
6.2 - 6.5 (2H, br.s, $-NH_2$)
7.61 (1H, d, $J_{5,6}$ = 9.5Hz, 6 - H)

Preparative Example 19

2 - Amino - 5 - dimethylaminopropiophenone

Using 26.1 g (0.19 mol) of 4 - dimethylaminoaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 18 whereby 4.86 g (13.2%) of the title compound is obtained.

MP 98.5 - 99.5 °C
IR(KBr): 3450, 3330, 2965, 2920, 2895, 2790, 1639, 1571, 1555, 1499, 1205.
NMR($CDCl_3$) δppm:
1.21 (3H, t, J = 7.3Hz, $-CH_2CH_3$)
2.83 (6H, s, $-N(CH_3)_2$)
2.98 (2H, q, $-CH_2CH_3$)
5.7 - 6.0 (2H, br.s, $-NH_2$)
6.64 (1H, d, $J_{3,4}$ = 8.8Hz, 3 - H)
6.98 (1H, dd, 4 - H)
7.14 (1H, d, $J_{4,6}$ = 2.2Hz, 6 - H)

Preparative Example 20

2,4 - Diaminopropiophenone and 2,6 - diaminopropiophenone

Using 19.9 g (0.19 mol) of 1,3 - phenylenediamine, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 18 whereby the title compounds, i.e. 5.20 g (17.0%) of 2,4 - diaminopropiophenone and 1.35 g (4.4%) of 2,6 - diaminopropiophenone, are obtained.

2,4 - Diaminopropiophenone

MP 155 - 157 °C
IR(KBr): 3410, 3330, 3210, 2970, 2920, 2900, 1615, 1566, 1527, 1439, 1374, 1236, 1155.
NMR($CDCl_3$) δppm:
1.18 (3H, t, J = 7.3Hz, $-CH_2CH_3$)
2.86 (2H, q, $-CH_2CH_3$)
5.81 (1H, d, $J_{3,5}$ = 2.2Hz, 3 - H)
5.96 (1H, dd, 5 - H)
7.56 (1H, d, $J_{5,6}$ = 8.1Hz, 6 - H)

2,6 - Diaminopropiophenone

MP 65 - 66.5 °C
IR(KBr): 3440, 3350, 1589, 1456, 1212.
NMR($CDCl_3$) δppm:
1.21 (3H, t, J = 7.3Hz, $-CH_2CH_3$)
2.93 (2H, q, $-CH_2CH_3$)
4.2 - 4.8 (4H, br. s, $-NH_2$x2)
6.06 (2H, d, J = 7.3Hz, 3 and 5 - H)
6.95 (1H, t, 4 - H)

Preparative Exampl 21

2 - Amino - 3 - fluoroacetophenone

Using 21.3 g (0.19 mol) of 2 - fluoroaniline and 15.7 g(0.38 mol) of acetonitrile, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 0.99 g (3.4%) of the title compound is obtained.

MP 60 - 61.5 °C

IR(KBr): 3440, 3350, 1629, 1551, 1452, 1262.

NMR($CDCl_3$) δ ppm:

2.58 (3H, s, $-CH_3$)
6.0 - 6.6 (2H, br.s, $-NH_2$)
6.57 (1H, m, 5 - H)
7.11 (1H, m, 4 - H)
7.51 (1H, dd, $J_{4,6}$ = 1.5Hz, $J_{5,6}$ = 8.1Hz, 6 - H)

Preparative Example 22

2 - Amino - 4 - bromoacetophenone

Using 33.0 g (0.19 mol) of 3 - bromoaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 21 whereby 14.39 g (34.9%) of the title compound is obtained.

MP 81.5 - 84.5 °C

IR(KBr): 3410, 3300, 1633, 1608, 1532, 1234.

NMR($CDCl_3$) δppm:

2.54 (3H, s, $-CH_3$)
6.1 - 6.5 (2H, br. s, $-NH_2$)
6.75 (1H, dd, $J_{3,5}$ = 1.5Hz, $J_{5,6}$ = 8.1Hz, 5 - H)
6.83 (1H, d, 3 - H)
7.54 (1H, d, 6 - H)

Preparative Example 23

2 - Amino - 5 - ethoxyacetophenone

Using 26.3 g (0.19 mol) of 4 - ethoxyaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 21 whereby 2.17 g (6.3%) of the title compound is obtained.

MP 94 - 95 °C

IR(KBr): 3450, 3330, 2965, 1634, 1561, 1551, 1200.

NMR($CDCl_3$) δ ppm:

1.40 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.56 (3H, s, $-CH_3$)
3.99 (2H, q, $-\underline{CH_2}CH_3$)
5.7 - 6.2 (2H, br.s, $-NH_2$)
6.62 (1H, d, $J_{3,4}$ = 8.8Hz, 3 - H)
6.97 (1H, dd, 4 - H)
7.20 (1H, d, $J_{4,6}$ = 2.9Hz, 6 - H)

Preparative Example 24

2 - Amino - 4 - chlorobutyrophenone

Using 24.5 g (0.19 mol) of 3 - chloroaniline and 26.5 g (0.38 mol) of butyronitrile, the reaction followed by th after - tr atment is carri d out in th sam manner as in Preparative Example 1 whereby 16.53 g (43.5%) of the title compound is obtained.

MP 44 - 46 °C

IR(KBr): 3450, 3340, 2960, 1639, 1609, 1577, 1537, 1423, 1203.

NMR($CDCl_3$) δppm:

1.00 (3H, t, J = 7.3Hz, $-CH_2CH_2CH_3$)
1.74 (2H, tq, J = 7.3Hz, $-CH_2CH_2CH_3$)
2.87 (2H, t, J = 7.3Hz, $-CH_2CH_2CH_3$)
6.36 (2H, br.s, $-NH_2$)
6.60 (1H, dd, $J_{3,5}$ = 2.2Hz, $J_{5,6}$ = 8.8Hz, 5 - H)
6.64 (1H, d, 3 - H)
7.66 (1H, d, 6 - H)

Preparative Example 25

2 - Amino - 5 - methylbutyrophenone

Using 20.6 g (0.19 mol) of 4 - methylaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 24 whereby 20.79 g (61.0%) of the title compound is obtained.

MP 65 - 67 °C
IR(KBr): 3440, 3330, 1632, 1575, 1557, 1547, 1222, 1186, 1160.
NMR($CDCl_3$) δppm:

1.01 (3H, t, J = 7.3Hz, $-CH_2CH_2CH_3$)
1.75 (2H, tq, J = 7.3Hz, $-CH_2CH_2CH_3$)
2.26 (3H, s, $-CH_3$)
2.90 (2H, t, J = 7.3Hz, $-CH_2CH_2CH_3$)
6.10 (2H, br.s, $-NH_2$)
6.58 (1H, d, $J_{3,4}$ = 8.1Hz, 3 - H)
7.08 (1H, dd, 4 - H)
7.52 (1H, d, $J_{4,6}$ = 1.5Hz, 6 - H)

Preparative Example 26

2 - Amino - 3 - bromoisobutyrophenone

Using 33.0 g (0.19 mol) of 2 - bromoaniline and 26.5 g (0.38 mol) of isobutyronitrile, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 4.38 g (9.4%) of the title compound is obtained as an oil.

IR(neat): 3450, 3320, 2960, 1646, 1602, 1561, 1531, 1217.
NMR($CDCl_3$) δppm:

1.20 (6H, d, J = 7.0Hz, $-CH(CH_3)_2$)
3.51 - 3.63 (1H, m, $-CH(CH_3)_2$)
6.53 (1H, dd, $J_{4,5}$ = 7.7Hz, $J_{5,6}$ = 8.1Hz, 5 - H)
6.93 (2H, br.s, $-NH_2$)
7.56 (1H, dd, $J_{4,6}$ = 1.5Hz, 4 - H)
7.75 (1H, dd, 6 - H)

Preparative Example 27

2 - Amino - 4 - methoxyisobutyrophenone and 2 - amino - 6 - methoxyisobutyrophenone

Using 23.7 g (0.19 mol) 3 - methoxyaniline, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 26 whereby the title compounds, i.e. 24.75 g (66.8%) of 2 - amino - 4 - methoxyisobutyrophenone and 2.40 g (6.5%) of 2 - amino - 6 - methoxyisobutyrophenone as an oil, are obtained.

2 - Amino - 4 - methoxyisobutyrophenone

MP 69 - 70 °C
IR(KBr): 3400, 3300, 2960, 1607, 1532, 1457, 1384, 1212, 1134.
NMR($CDCl_3$) δ ppm:

1.19 (6H, d, J = 7.0Hz, $-CH(CH_3)_2$)
3.51 (1H, qq, $-CH(CH_3)_2$)
3.80 (3H, s, $-OCH_3$)
6.08 (1H, d, $J_{3,5}$ = 2.6Hz, 3 - H)
6.23 (1H, dd, 5 - H)
6.45 (2H, br.s, $-NH_2$)
7.70 (1H, d, $J_{5,6}$ = 9.2Hz, 6 - H)

2 - Amino - 6 - methoxyisobutyrophenone

IR(neat): 3460, 3360, 2960, 1609, 1576, 1465, 1268, 1133.
NMR($CDCl_3$) δppm:
1.12 (6H, d, J = 7.0Hz, $-CH(CH_3)_2$)
3.49 (1H, qq, $-CH(CH_3)_2$)
3.81 (3H, s, $-OCH_3$)
5.12 (2H, br.s, $-NH_2$)
6.22 (1H, dd, $J_{3,4}$ = 8.1Hz, $J_{3,5}$ = 1.1Hz, 3 - H)
6.26 (1H, dd, $J_{4,5}$ = 8.1Hz, 5 - H)
7.08 (1H, dd, 4 - H)

Preparative Example 28

2 - Amino - 5 - bromovalerophenone

Using 33.0 g (0.19 mol) of 4 - bromoaniline and 31.8 g (0.38 mol) of valeronitrile, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 1 whereby 10.70 g (21.8%) of the title compound is obtained.

MP 74 - 76 °C
IR(KBr): 3440, 3330, 2950, 1640, 1609, 1581, 1530, 1194.
NMR($CDCl_3$) δppm:
0.96 (3H, t, J = 7.3Hz, $-CH_2CH_2CH_2CH_3$)
1.34 - 1.46 (2H, m, $-CH_2CH_2CH_2CH_3$)
1.63 - 1.74 (2H, m, $CH_2CH_2CH_2CH_3$)
2.89 (2H, t, J = 7.3Hz, $-CH_2CH_2CH_2CH_3$)
6.29 (2H, br.s, $-NH_2$)
6.55 (1H, d, $J_{3,4}$ = 8.8Hz, 3 - H)
7.31 (1H, dd, 4 - H)
7.82 (1H, d, $J_{4,6}$ = 2.6Hz, 6 - H)

Preparative Example 29

2 - Amino - 5 - nitropropiophenone

1.0 g (6.7 mmol) of 2 - aminopropiophenone is dissolved in 15 ml of concentrated sulfuric acid, and 1 ml of a solution of 746 mg (7.4 mmol) potassium nitrate in concentrated sulfuric acid is added dropwise at - 10 °C over 30 minutes and the mixture is stirred at - 10 °C for 30 minutes. After the reaction, the reaction solution is poured into ice - water and the mixture is extracted three times each with 200 ml of chloroform, and the extracts are combined and dried over anhydrous magnesium sulfate. The solvent is distilled off under reduced pressure, and the residue is subjected to column chromatography on silica gel (eluent: ether - n - hexane 1:1) and then recrystallized from ether whereby 30 mg (2.3%) of the title compound is obtained.

MP 74.5 - 76 °C
IR(KBr): 3410, 3050, 2970, 2920, 1634, 1527, 1502, 1337.
NMR($CDCl_3$) δ ppm:
1.55 (3H, t, J = 7.3Hz, $-CH_2CH_3$)
3.31 (2H, q, $-CH_2CH_3$)
7.64 (1H, d, $J_{3,4}$ = 9.5Hz, 3 - H)
8.06 (1H, dd, 4 - H)

8.63 (1H, d, $J_{4,6}$ = 2.2Hz, 6 - H)

Preparative Example 30

2 - Amino - 4 - cyanopropiophenone

10.0 g (43.8 mmol) of 2 - amino - 4 - bromopropiophenone obtained in Preparative Example 3 is dissolved in 10 ml of dimethylformamide, and 4.3 g (48.2 mmol) of cuprous cyanide is added. The mixture is stirred at 170° C for 2 hours in nitrogen atmosphere. After cooling, chloroform is added to the reaction mixture and insoluble matters are filtered off. The filtrate is extracted several times with chloroform. The chloroform extracts are combined, washed with water, dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue obtained is isolated and purified by column chromatography on silica gel (eluent: chloroform - n - hexane 1:1) and then recrystallized from ether - n - hexane whereby 4.4 g (58.0%) of the title compound is obtained.

MP 118 - 120° C

IR(KBr): 3430, 3320, 2225, 1651, 1610, 1581, 1204.

NMR($CDCl_3$) δppm:

1.21 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.98 (2H, q, $-\underline{CH_2}CH_3$)
6.43 (2H, br.s, $-\overline{NH_2}$)
6.87 (1H, dd, $J_{3,5}$ = 1.5Hz, $J_{5,6}$ = 8.8Hz, 5 - H)
6.94 (1H, d, 3 - H)
7.82 (1H, d, 6 - H)

Preparative Example 31

2 - Amino - 5 - cyanopropiophenone

Using 2.3 g (10.0 mmol) 2 - amino - 5 - bromopropiophenone, 1.0 g (11.0 mmol) of cuprous cyanide and 2.3 ml of dimethylformamide, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 30 whereby 0.78 g (44.8%) of the title compound is obtained.

MP 130.5 - 131.5° C

IR(KBr): 3420, 3310, 2215, 1625.

NMR($CDCl_3$) δppm:

1.22 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.97 (2H, q, $-\underline{CH_2}CH_3$)
6.45 - 7.20 (2H, $\overline{br}$, $-NH_2$)
6.67 (1H, d, $J_{3,4}$ = 8.4Hz, 3 - H)
7.44 (1H, dd, 4 - H)
8.08 (1H, d, $J_{4,6}$ = 1.8Hz, 6 - H)

Preparative Example 32

2,5 - Diaminopropiophenone

Using 19.9 g (0.19 mol) of 1,4 - phenylenediamine, the reaction followed by the after - treatment is carried out in the same manner as in Preparative Example 18 whereby 7.30 g (23.8%) of the title compound is obtained.

MP 132 - 135° C

IR(KBr): 3380, 3378, 3220, 2960, 2915, 2900, 1644, 1562, 1491, 1263, 1199.

NMR($CDCl_3$) δ ppm:

1.20 (3H, t, J = 7.3Hz, $-CH_2\underline{CH_3}$)
2.93 (2H, q, $-\underline{CH_2}CH_3$)
6.57 (1H, d, $J_{3,4}$ = 8.8Hz, 3 - H)
6.78 (1H, dd, 4 - H)
7.11 (1H, d, $J_{4,6}$ = 2.2Hz, 6 - H)

Preparativ Example 33

2 - Amino - 4 - fluoro - 5 - methoxypropiophenone

Using 3 - fluoro - 4 - methoxyaniline (27.1 g, 0.19 mol), the reaction followed by the after - treatment is carried out in the same manner as Preparative Example 1 whereby 26.4 g (69.7%) of the title compound is obtained.

MP 96.5 - 97.5 °C

IR(KBr)cm : 3420, 3325, 1644, 1590, 1555, 1507, 1241, 1197, 1150.

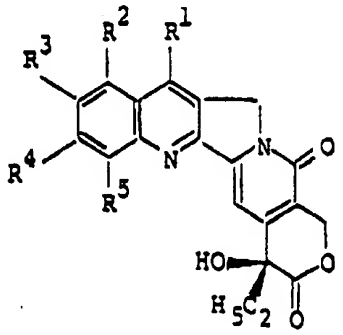
NMR($CDCl_3$) δ ppm:

1.21 (3H, t, J = 7.3Hz, $-COCH_2\underline{CH_3}$)
2.92 (2H, q, $-COCH_2CH_3$)
3.85 (3H, s, $-OCH_3$)
6.07 - 6.28 (2H, br, $-NH_2$)
6.39 (1H, d, $J_{3,F}$ = 12.8Hz, 3 - H)
7.31 (1H, d, $J_{6,F}$ = 9.5Hz, 6 - H)

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Camptothecin derivatives represented by the general formula:



(I)

wherein R^1 represents a $C_1 - C_8$ alkyl group, R^2 represents a hydrogen atom or an amino, hydroxyl, $C_1 - C_8$ acylamino or $C_1 - C_8$ alkoxy group, R^3 represents a hydrogen or halogen atom or a $C_1 - C_8$ alkyl, hydroxyl, $C_1 - C_8$ alkoxy, nitro, amino, cyano or di($C_1 - C_8$ alkyl)amino group, R^4 represents a hydrogen or halogen atom or a $C_1 - C_8$ alkyl, hydroxyl, $C_1 - C_8$ alkoxy, $C_1 - C_8$ alkylthio, amino, cyano, $C_1 - C_8$ alkylamino or di($C_1 - C_8$ alkyl)amino group, and R^5 represents a hydrogen or halogen atom or a hydroxyl or $C_1 - C_8$ alkoxy group, with the proviso that not all of the R^2, R^3, R^4 and R^5 substituents are simultaneously a hydrogen atom and also that if any one of the R^2, R^3, R^4 and R^5 is a hydroxyl or $C_1 - C_8$ alkoxy group, not all of the other three substituents are simultaneously a hydrogen atom.

2. Camptothecin derivatives according to claim 1, wherein any one of the R^2, R^3, R^4 and R^5 substituents is a halogen atom and the other substituents are hydrogen atoms.

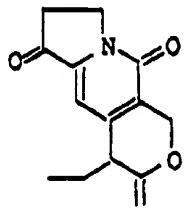
3. Camptothecin derivatives according to claim 2, wherein the halogen atom is a fluorine atom.

4. Camptothecin derivatives according to claim 2, wherein the halogen atom is a chlorine atom.

5. Camptothecin derivatives according to claim 2, wherein the halogen atom is a bromine atom.

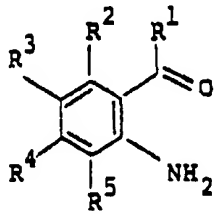
6. Camptothecin derivatives according to claim 1, wherein any two of th R^2, R^3, R^4 and R^5 substituents are hydroxyl and/or lower alkoxy group and th other substituents are hydrogen atoms.

7. A process for the preparation of the camptothecin derivatives of the general formula I according to claim 1 which comprises condensing 1,5-dioxo(5'-ethyl-2'H,5'H,6'H-6-oxopyrano)[3',4'-f]-Δ6-(8)-tetrahydroindolidine of the formula;



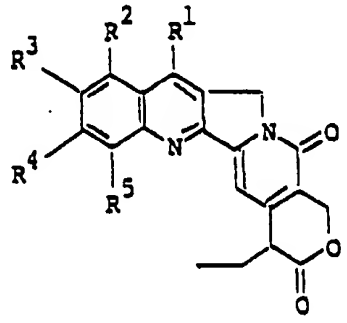
(II)

with an o-acyl-aniline compound of the general formula:



(III)

wherein R^1, R^2, R^3, R^4 and R^5 have the same meanings as given above,
and oxidizing the resultant 20-deoxy-camptothecin derivative of the general formula:



(IV)

wherein R^1, R^2, R^3, R^4 and R^5 have the same meanings as given above,
with oxygen in the presence of cupric ion, and if desired, converting in the resultant camptothecin derivative of the general formula (I) any alkoxy group into the free hydroxyl group and any free amino group into a lower acylamino group.

8. A process according to claim 7, wherein the compound of the formula (II) is condensed with the compound of the general formula (III) under reflux in an inert solvent in the presence of a dehydration catalyst.

9. A process according to claim 7, wherein the lower alkoxy group in the resultant camptothecin derivatives is converted into th free hydroxyl group by dealkylation conducted in an inert solvent with an aluminum halide or und r r flux in a concentrated hydrohalic acid.

10. A process according to claim 7, wh rein the amino group in the resultant camptoth cin derivatives is converted into a lower acyl group by N-acylation conduct d in the presence of a tertiary amine with

an exc ss amount of a lower acylating agent.

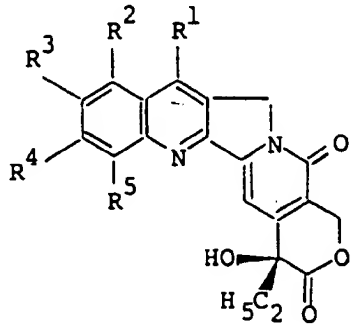
11. A camptothecin derivative of the general formula I according to any one of claims 1 to 6 for use as a medicament.

12. A camptothecin derivative of the general formula I according to any one of claims 1 to 6 for use as an anti-tumor medicament.

13. Pharmaceutical composition comprising a camptothecin derivative of the general formula I according to any one of claims 1 to 6 and a physiologically acceptable carrier.

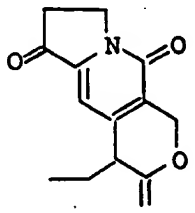
Claims for the following Contracting State : ES

1. A process for the preparation of new camptothecin derivatives of the general formula I



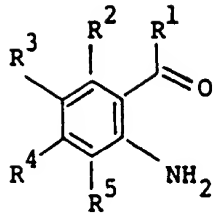
(I)

wherein R^1 represents a C_1-C_8 alkyl group, R^2 represents a hydrogen atom or an amino, hydroxyl, C_1-C_8 acylamino or C_1-C_8 alkoxy group, R^3 represents a hydrogen or halogen atom or a C_1-C_8 alkyl, hydroxyl, C_1-C_8 alkoxy, nitro, amino, cyano or di(C_1-C_8 alkyl)amino group, R^4 represents a hydrogen or halogen atom or a C_1-C_8 alkyl, hydroxyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, amino, cyano, C_1-C_8 alkylamino or di(C_1-C_8 alkyl)amino group, and R^5 represents a hydrogen or halogen atom or a hydroxyl or C_1-C_8 alkoxy group, with the proviso that not all of the R^2, R^3, R^4 and R^5 substituents are simultaneously a hydrogen atom and also that if any one of the R^2, R^3, R^4 and R^5 is a hydroxyl or C_1-C_8 alkoxy group, not all of the other three substituents are simultaneously a hydrogen atom, which comprises condensing 1,5-dioxo(5'-ethyl-2'H,5'H,6'H-6-oxopyrano)[3',4'-f]-Δ6(8)-tetrahydroindolidine of the formula:



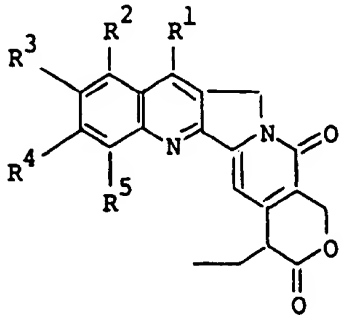
(II)

with an o-acyl-aniline compound of the general formula:



(III)

wherein R^1, R^2, R^3, R^4 and R^5 have the same meanings as given above,
and oxidizing the resultant 20-deoxy-camptothecin derivative of the general formula:



(IV)

wherein R^1, R^2, R^3, R^4 and R^5 have the same meanings as given above,
with oxygen in the presence of cupric ion, and if desired, converting in the resultant camptothecin derivative of the general formula (I) any alkoxy group into the free hydroxyl group and any free amino group into a C_1-C_8 acylamino group.

2. A process according to claim 1 whereby in the camptothecin derivatives any one of the R^2, R^3, R^4 and R^5 substituents is a halogen atom and the other substituents are hydrogen atoms.

3. A process according to claim 2 whereby in the camptothecin derivatives the halogen atom is a fluorine atom.

4. A process according to claim 2 whereby in the camptothecin derivatives the halogen atom is a chlorine atom.

5. A process according to claim 2 whereby in the camptothecin derivatives the halogen atom is a bromine atom.

6. A process according to claim 1 whereby in the camptothecin derivatives any two of the R^2, R^3, R^4 and R^5 substituents are hydroxyl and/or C_1-C_8 alkoxy group and the other substituents are hydrogen atoms.

7. A process according to any one of claims 1 to 6, wherein the compound of the formula (II) is condensed with the compound of the general formula (III) under reflux in an inert solvent in the presence of a dehydration catalyst.

8. A process according to any one of claims 1 to 6, wherein the lower alkoxy group in the resultant camptothecin derivatives is converted into the free hydroxyl group by dealkylation conducted in an inert solvent with an aluminum halide or under r flux in a concentrated hydrohalic acid.

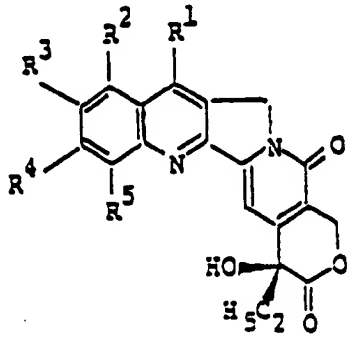
9. A process according to any one of claims 1 to 6, wherein th amino group in the r sultant camptothecin derivatives is converted into a C_1-C_8 acyl group by N-acylation conducted in the

pr sence of a tertiary amine with an excess amount of a $C_1 - C_8$ acylating agent.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Camptothecin - Derivate der allgemeinen Formel:



(I)

wobei R^1 ein $C_1 - C_8$ - Alkylrest ist, R^2 ein Wasserstoffatom oder ein Amino -, Hydroxyl -, $C_1 - C_8$ - Acylamino - oder $C_1 - C_8$ - Alkoxyrest ist, R^3 ein Wasserstoff - oder Halogenatom oder ein $C_1 - C_8$ - Alkyl -, Hydroxyl -, $C_1 - C_8$ - Alkoxy -, Nitro -, Amino -, Cyan - oder Di($C_1 - C_8$ - alkyl) - aminorest ist, R^4 ein Wasserstoff - oder Halogenatom oder ein $C_1 - C_8$ - Alkyl -, Hydroxyl -, $C_1 - C_8$ - Alkoxy -, $C_1 - C_8$ - Alkylthio -, Amino -, Cyan -, $C_1 - C_8$ - Alkylamino oder Di($C_1 - C_8$ - alkyl)aminorest ist, R^5 ein Wasserstoff - oder Halogenatom oder ein Hydroxyl - oder $C_1 - C_8$ - Alkoxyrest ist, mit der Maßgabe, daß nicht alle der R^2 -, R^3 -, R^4 - und R^5 - Substituenten gleichzeitig ein Wasserstoffatom sind und ebenso, daß, falls ein R^2, R^3, R^4 und R^5 ein Hydroxyl - oder $C_1 - C_8$ - Alkoxyrest ist, nicht alle anderen drei Substituenten gleichzeitig ein Wasserstoffatom sind.

2. Camptothecin - Derivate gemäß Anspruch 1, wobei einer der R^2 -, R^3 -, R^4 - und R^5 - Substituenten ein Halogenatom ist und die anderen Substituenten Wasserstoffatome sind.

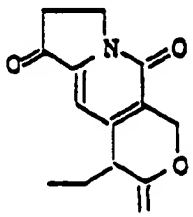
3. Camptothecin - Derivate gemäß Anspruch 2, wobei das Halogenatom ein Fluoratom ist.

4. Camptothecin - Derivate gemäß Anspruch 2, wobei das Halogenatom ein Chloratom ist.

5. Camptothecin - Derivate gemäß Anspruch 2, wobei das Halogenatom ein Bromatom ist.

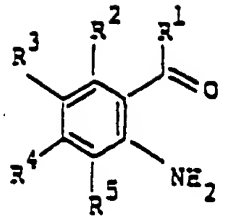
6. Camptothecin - Derivate gemäß Anspruch 1, wobei zwei der R^2 -, R^3 -, R^4 - und R^5 - Substituenten Hydroxyl - und/oder Niederalkoxyreste und die anderen Substituenten Wasserstoffatome sind.

7. Verfahren zur Herstellung von Camptothecin - Derivaten der allgemeinen Formel I gemäß Anspruch 1, welches die Kondensation von 1,5 - Dioxo(5' - ethyl - 2'H,5'H,6'H - 6 - oxopyrano) - [3',4' - f] - Δ6(8) - tetrahydroindolidin der Formel:



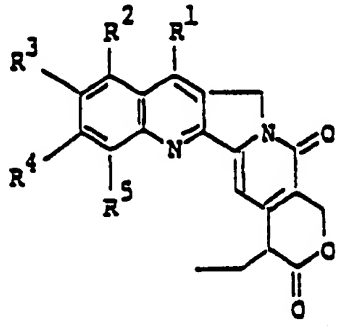
(II)

mit einer o - Acylanilin - Verbindung der allgemeinen Formel:



(III)

umfaßt, wobei R^1, R^2, R^3, R^4 und R^5 die gleiche Bedeutung, wie vorstehend erwähnt, haben, sowie Oxidation des entstandenen 20 - Deoxycamptothecin - Derivats der allgemeinen Formel:



(IV)

wobei R^1, R^2, R^3, R^4 und R^5 die gleiche Bedeutung, wie vorstehend erwähnt, haben,

mit Sauerstoff in Gegenwart von Kupferionen, und wenn gewünscht, Überführung von jedem Alkoxyrest in die freie Hydroxylgruppe und jeder freien Aminogruppe in einen Niederacylaminorest im entstandenen Camptothecin - Derivat der allgemeinen Formel (I).

8. Verfahren gemäß Anspruch 7, wobei die Verbindung der Formel (II) mit einer Verbindung der allgemeinen Formel (III) unter Rückfluß in einem inerten Lösemittel in Gegenwart eines Dehydratationskatalysators kondensiert wird.

9. Verfahren gemäß Anspruch 7, wobei der Niederalkoxyrest in den erhaltenen Camptothecin - Derivaten in die freie Hydroxylgruppe durch Dealkylierung überführt wird, durchgeführt in einem inerten Lösemittel mit einem Aluminiumhalogenid oder unter Rückfluß in einer konzentrierten Halogenwasserstoffsäure.

10. Verfahren gemäß Anspruch 7, wobei die Aminogruppe in den erhaltenen Camptothecin - Derivaten in einen Niederacylrest durch N - Acylierung überführt wird, durchgeführt in Gegenwart eines tertiären Amins mit einem Überschuß eines niederen Acylierungsmittels.

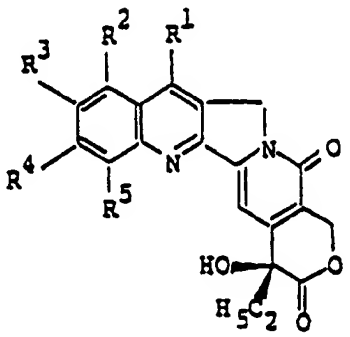
11. Camptothecin - Derivat der allgemeinen Formel I gemäß einem der Ansprüche 1 bis 6 zur Verwendung als Arzneimittel.

12. Camptothecin - Derivat der allgemeinen Formel I gemäß einem der Ansprüche 1 bis 6 zur Verwendung als Antitumor - Arzneimittel.

13. Arzneimittel umfassend ein Camptothecin - Derivat der allgemeinen Formel I gemäß einem der Ansprüche 1 bis 6 und einen physiologisch verträglichen Träger.

Patentansprüche für folgend n Vertragsstaat : ES

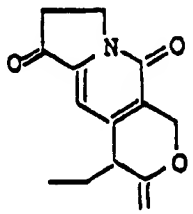
1. Verfahren zur Herstellung von neuen Camptothecin - Derivaten der allgemeinen Formel I:



(I)

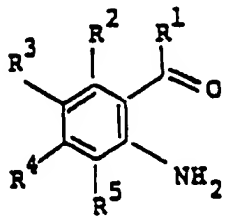
wobei R^1 ein C_1 - C_8 - Alkylrest ist, R^2 ein Wasserstoffatom oder ein Amino -, Hydroxyl -, C_1 - C_8 - Acylamino - oder C_1 - C_8 - Alkoxyrest ist, R^3 ein Wasserstoff - oder Halogenatom oder ein C_1 - C_8 - Alkyl -, Hydroxyl -, C_1 - C_8 - Alkoxy -, Nitro -, Amino -, Cyan - oder Di(C_1 - C_8 - alkyl) - aminorest ist, R^4 ein Wasserstoff - oder Halogenatom oder ein C_1 - C_8 - Alkyl -, Hydroxyl -, C_1 - C_8 - Alkoxy -, C_1 - C_8 - Alkylthio -, Amino -, Cyan -, C_1 - C_8 - Alkylamino oder Di(C_1 - C_8 - alkyl)aminorest ist, R^5 ein Wasserstoff - oder Halogenatom oder ein Hydroxyl - oder C_1 - C_8 - Alkoxyrest ist, mit der Maßgabe, daß nicht alle der R^2 -, R^3 -, R^4 - und R^5 - Substituenten gleichzeitig ein Wasserstoffatom sind und ebenso, daß, falls ein R^2, R^3, R^4 und R^5 ein Hydroxyl - oder C_1 - C_8 - Alkoxyrest ist, nicht alle anderen drei Substituenten gleichzeitig ein Wasserstoffatom sind,

welches die Kondensation von 1,5 - Dioxo(5' - ethyl - 2'H,5'H,6'H - 6 - oxopyrano)[3',4' - f] - Δ6(8) - tetrahydroindolidin der Formel:



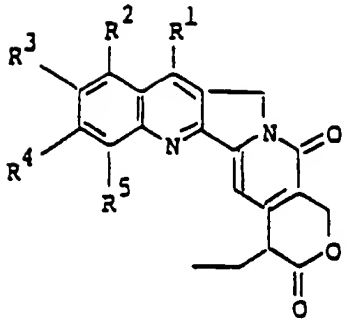
(II)

mit einer o - Acylanilin - Verbindung der allgemeinen Formel:



(III)

umfaßt, wobei R^1, R^2, R^3, R^4 und R^5 die gleiche Bedeutung, wie vorstehend erwähnt, haben, sowie Oxidation des entstandenen 20 - Deoxycamptothecin - Derivats der allgemeinen Formel:



(IV)

wobei R^1, R^2, R^3, R^4 und R^5 die gleiche Bedeutung, wie vorstehend erwähnt, haben,

mit Sauerstoff in Gegenwart von Kupferionen, und wenn gewünscht, Überführung von jedem Alkoxyrest in die freie Hydroxylgruppe und jeder freien Aminogruppe in einen Niederacylaminorest im entstandenen Camptothecin - Derivat der allgemeinen Formel (I).

2. Verfahren gemäß Anspruch 1, wobei in den Camptothecin - Derivaten einer der R^2 -, R^3 -, R^4 - und R^5 - Substituenten ein Halogenatom ist und die anderen Substituenten Wasserstoffatome sind.

3. Verfahren gemäß Anspruch 2, wobei in den Camptothecin - Derivaten das Halogenatom ein Fluoratom ist.

4. Verfahren gemäß Anspruch 2, wobei in den Camptothecin - Derivaten das Halogenatom ein Chloratom ist.

5. Verfahren gemäß Anspruch 2, wobei in den Camptothecin - Derivaten das Halogenatom ein Bromatom ist.

6. Verfahren gemäß Anspruch 1, wobei in den Camptothecin - Derivaten zwei der R^2 -, R^3 -, R^4 - und R^5 - Substituenten Hydroxyl - und/oder Niederalkoxyreste und die anderen Substituenten Wasserstoffatome sind.

7. Verfahren gemäß einem der Ansprüche 1 - 6, wobei die Verbindung der Formel (II) mit einer Verbindung der allgemeinen Formel (III) unter Rückfluß in einem inerten Lösemittel in Gegenwart eines Dehydratationskatalysators kondensiert wird.

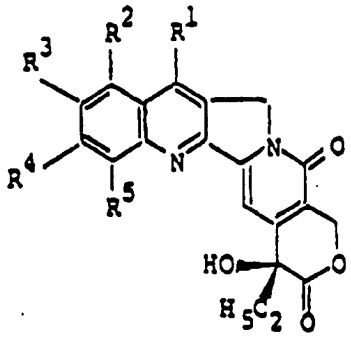
8. Verfahren gemäß einem der Ansprüche 1 - 6, wobei der Niederalkoxyrest in den erhaltenen Camptothecin - Derivaten in die freie Hydroxylgruppe durch Dealkylierung überführt wird, durchgeführt in einem inerten Lösemittel mit einem Aluminiumhalogenid oder unter Rückfluß in einer konzentrierten Halogenwasserstoffsäure.

9. Verfahren gemäß einem der Ansprüche 1 - 6, wobei die Aminogruppe in den erhaltenen Camptothecin - Derivaten in einen C_1 - C_8 - Acylrest durch N - Acylierung überführt wird, durchgeführt in Gegenwart eines tertiären Amins mit einem Überschuß eines C_1 - C_8 - Acylierungsmittels.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Dérivés de camptothécine représentés par la formule générale :



(I)

dans laquelle R^1 représente un groupe alkyle en $C_1 - C_8$, R^2 représente un atome d'hydrogène ou un groupe amino, hydroxyle, acylamino en $C_1 - C_8$ ou alcoxy en $C_1 - C_8$, R^3 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle en $C_1 - C_8$, hydroxyle, alcoxy en $C_1 - C_8$, nitro, amino, cyano ou di(alkyl en $C_1 - C_8$)amino, R^4 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle en $C_1 - C_8$, hydroxyle, alcoxy en $C_1 - C_8$, alkylthio en $C_1 - C_8$, amino, cyano, alkylamino en $C_1 - C_8$ ou di(alkyl en $C_1 - C_8$)amino et R^5 représente un atome d'hydrogène ou d'halogène ou un groupe hydroxyle ou alcoxy en $C_1 - C_8$, sous réserve que tous les substituants R^2, R^3, R^4 et R^5 ne soient pas simultanément un atome d'hydrogène, et également que si l'un quelconque de R^2, R^3, R^4 et R^5 est un groupe hydroxyle ou alcoxy en $C_1 - C_8$, les trois autres substituants ne soient pas tous simultanément un atome d'hydrogène.

2. Dérivés de camptothécine selon la revendication 1, dans lesquels l'un quelconque des substituants R^2, R^3, R^4 et R^5 est un atome d'halogène et les autres substituants sont des atomes d'hydrogène.

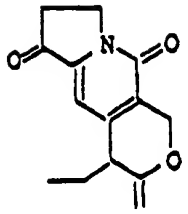
3. Dérivés de camptothécine selon la revendication 2, dans lesquels l'atome d'halogène est un atome de fluor.

4. Dérivés de camptothécine selon la revendication 2, dans lesquels l'atome d'halogène est un atome de chlore.

5. Dérivés de camptothécine selon la revendication 2, dans lesquels l'atome d'halogène est un atome de brome.

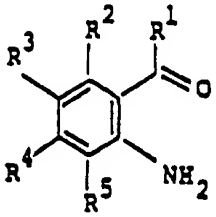
6. Dérivés de camptothécine selon la revendication 1, dans lesquels deux quelconques des substituants R^2, R^3, R^4 et R^5 sont un groupe hydroxyle et/ou alcoxy inférieur et les autres substituants sont des atomes d'hydrogène.

7. Un procédé pour la préparation des dérivés de camptothécine de formule générale (I) selon la revendication 1, qui comprend la condensation de la 1,5 - dioxo(5' - éthyl - 2'H,5'H,6'H - 6 - oxo - pyranno)[3',4' - f] - Δ6(8) - tétrahydro - indolidine de formule :



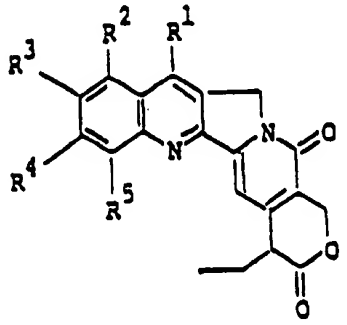
(II)

avec un composé de type o-acyl-aniline de formule générale :



(III)

dans laquelle R^1 R^2, R^3, R^4 et R^5 ont les mêmes significations que ci-dessus,
et l'oxydation du dérivé de type 20-désoxy-camptothécine obtenu de formule générale :



(IV)

dans laquelle R^1, R^2, R^3, R^4 et R^5 ont les mêmes significations que ci-dessus,
avec de l'oxygène en présence d'ion cuivrique et, si on le désire, la conversion, dans le dérivé de camptothécine obtenu de formule générale (I), d'un groupe alcoxy quelconque en le groupe hydroxyle libre et d'un groupe amino libre quelconque en un groupe acylamino inférieur.

8. Un procédé selon la revendication 7, dans lequel le composé de formule (II) est condensé avec le composé de formule générale (III) sous reflux dans un solvant inerte en présence d'un catalyseur de déshydratation.

9. Un procédé selon la revendication 7, dans lequel le groupe alcoxy inférieur, dans les dérivés de camptothécine obtenus, est transformé en le groupe hydroxyle libre par désalkylation effectuée dans un solvant inerte avec un halogénure d'aluminium ou sous reflux dans un hydracide halogéné concentré.

10. Un procédé selon la revendication 7, dans lequel le groupe amino des dérivés de camptothécine obtenus est transformé en un groupe acyle inférieur par N-acylation effectuée en présence d'une amine tertiaire avec un excès d'un agent d'acylation inférieure.

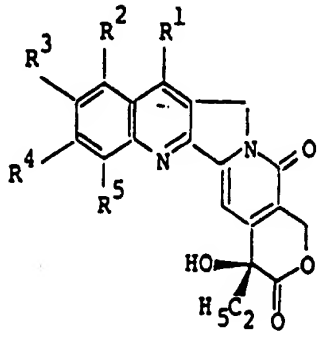
11. Un dérivé de camptothécine de formul générale (I) selon l'une quelconque des revendications 1 à 6 pour l'utilisation comm médicam nt.

12. Un dérivé de camptothécine de formule générale (I) selon l'une quelconque des revendications 1 à 6 pour l'utilisation comme médicament antitumoral.

13. Composition pharmaceutique comprenant un dérivé de camptothécine de formule générale (I) selon l'une quelconque des revendications 1 à 6 et un véhicule physiologiquement acceptable.

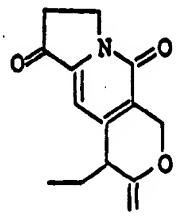
Revendications pour l'Etat contractant suivant : ES

1. Un procédé pour la préparation de nouveaux dérivés de camptothécine de formule générale (I) :



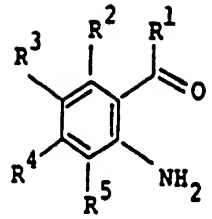
(I)

acquelle R^1 représente un groupe alkyle en C_1-C_8, R^2 représente un atome d'hydrogène ou un groupe amino, hydroxyle, acylamino en C_1-C_8 ou alcoxy en C_1-C_8, R^3 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle en C_1-C_8, hydroxyle, alcoxy en C_1-C_8, nitro, amino, cyano ou di(alkyl en C_1-C_8)amino, R^4 représente un atome d'hydrogène ou d'halogène ou un groupe alkyle en C_1-C_8,hydroxyle, alcoxy en C_1-C_8, alkylthio en C_1-C_8, amino, cyano, alkylamino en C_1-C_8 ou di(alkyl en C_1-C_8)amino et R^5 représente un atome d'hydrogène ou d'halogène ou un groupe hydroxyle ou alcoxy en C_1-C_8, sous réserve que tous les substituants R^2, R^3, R^4 et R^5 ne soient pas simultanément un atome d'hydrogène, et également que si l'un quelconque de R^2, R^3, R^4 et R^5 est un groupe hydroxyle ou alcoxy en C_1-C_8, les trois autres substituants ne soient pas tous simultanément un atome d'hydrogène,
qui comprend la condensation de la 1,5-dioxo(5'-éthyl-2'H,5'H,6'H-6-oxo-pyranno)[3',4'-f]-Δ6(8)-tétrahydro-indolidine de formule :



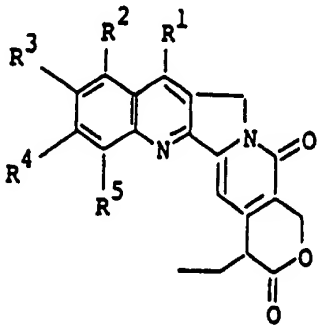
(II)

avec un composé de type o-acyl-aniline de formule générale :



(III)

dans laquelle R^1, R^2, R^3, R^4 et R^5 ont les mêmes significations que ci-dessus,
et l'oxydation du dérivé de type 20-désoxy-camptothécine obtenu de formule générale :



(IV)

dans laquelle R^1, R^2, R^3, R^4 et R^5 ont les mêmes significations que ci-dessus,
avec de l'oxygène en présence d'ion cuivrique et, si on le désire, la conversion, dans le dérivé de camptothécine obtenu de formule générale (I), d'un groupe alcoxy quelconque en le groupe hydroxyle libre et d'un groupe amino libre quelconque en un groupe acylamino en C_1-C_8.

2. Un procédé selon la revendication 1 où, dans les dérivés de camptothécine, l'un quelconque des substituants R^2, R^3, R^4 et R^5 est un atome d'halogène et les autres substituants sont des atomes d'hydrogène.

3. Un procédé selon la revendication 2 où, dans les dérivés de camptothécine, l'atome d'halogène est un atome de fluor.

4. Un procédé selon la revendication 2 où, dans les dérivés de camptothécine, l'atome d'halogène est un atome de chlore.

5. Un procédé selon la revendication 2 où, dans les dérivés de camptothécine, l'atome d'halogène est un atome de brome.

6. Un procédé selon la revendication 1 où, dans les dérivés de camptothécine, deux quelconques des substituants R^2, R^3, R^4 et R^5 sont un groupe hydroxyle et/ou alcoxy en C_1-C_8 et les autres substituants sont des atomes d'hydrogène.

7. Un procédé selon l'une quelconque des revendications 1 à 6, dans lequel le composé de formule (II) est condensé avec le composé de formule générale (III) sous reflux dans un solvant inerte en présence d'un catalyseur de déshydratation.

8. Un procédé selon l'une quelconque des revendications 1 à 6, dans lequel le groupe alcoxy inférieur, dans les dérivés de camptothécin obtenus, est transformé en le group hydroxyl libr par désalky-lation effectuée dans un solvant inerte avec un halogénur d'aluminium ou sous r flux dans un hydracide halogéné concentré.

9. Un procédé selon l'une quelconque des revendications 1 à 6, dans lequel le groupe amino des dérivés de camptothécin obtenus est transformé n un group acyle en $C_1 - C_8$ par N - acylation effectuée en présence d'une amine tertiaire avec un excès d'un agent d'acylation en $C_1 - C_8$.